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SYMPOSIUM ON THE LUNG

Editors: C. J. HULL
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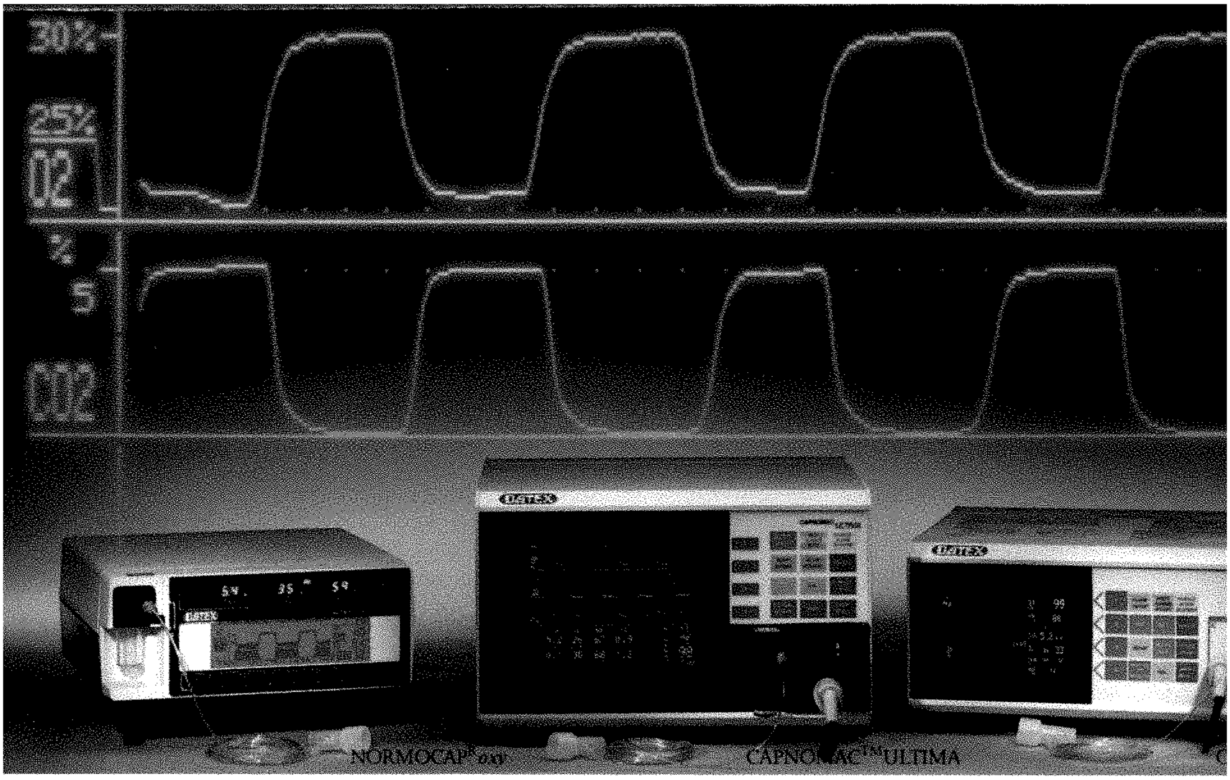

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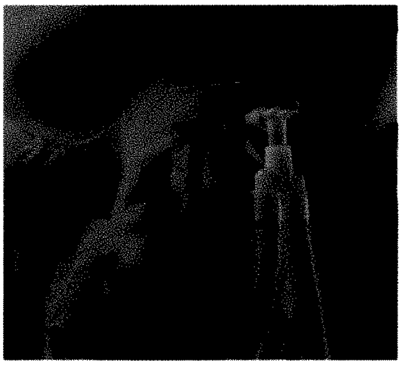

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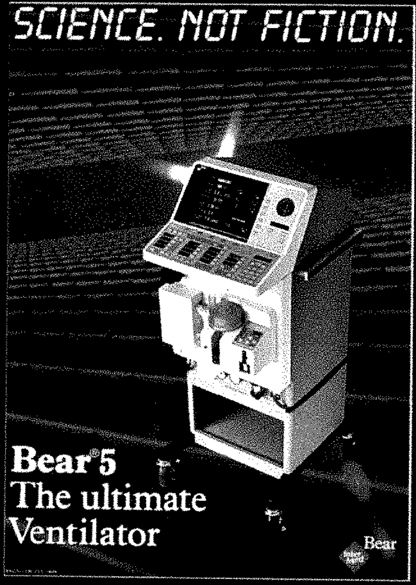

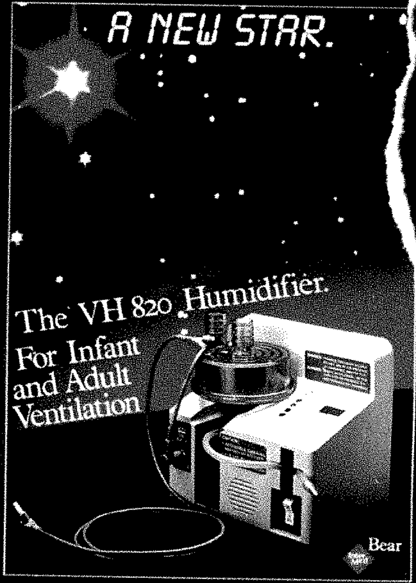

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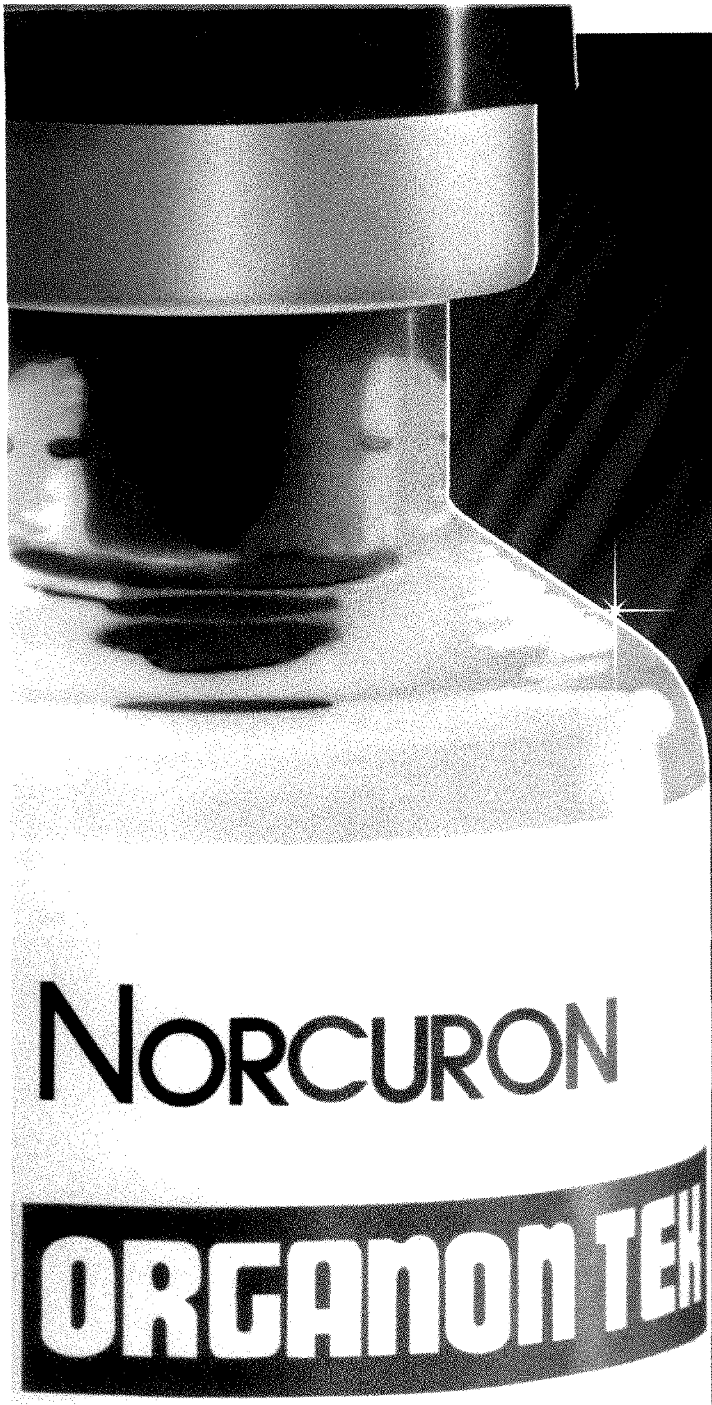

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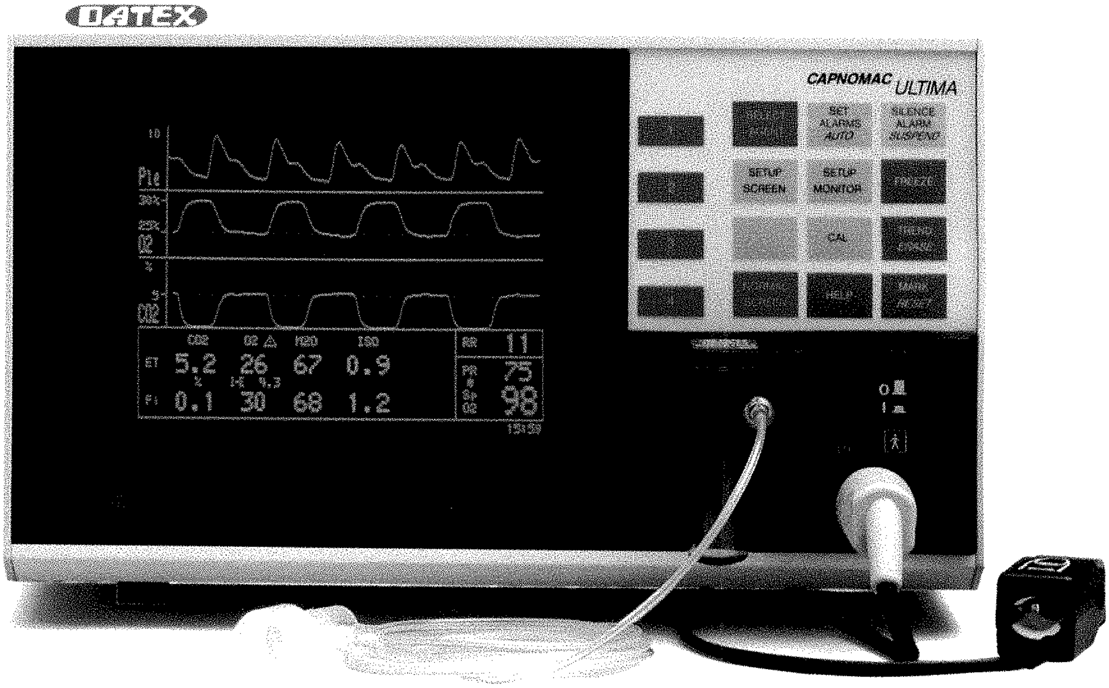

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EDITORIAL

THE INFLUENCE OF RESPIRATORY RESEARCH ON CLINICAL PROGRESS

A previous editorial [9] examined some areas of respiratory research which might lead to practical applications in anaesthetic practice. These included research into upper and lower airway obstruction, the function of respiratory muscles, the control of breathing and adult respiratory distress syndrome (ARDS). At that time it was becoming obvious that profound postoperative hypoxaemia could occur during sleep because of obstructive apnoea. That research was carried out at the Clinical Research Centre, Northwick Park, with experimental equipment which included a large, cumbersome oximeter. At that time it was inconceivable that a similar study might be performed a few years later in a District General Hospital with a portable system and half the number of investigators [17]. The availability of computed tomography and the development of simple compact instruments such as pulse oximeters and portable computers has greatly facilitated clinical research, so this is an appropriate time to review progress.

The old problem of "what causes the gas exchange abnormality during general anaesthesia?" seems to have been solved. Using computed tomography, Hedenstierna and colleagues [7] showed that dependent lung atelectasis develops during anaesthesia and the consequent gas exchange abnormality can be explained by the magnitude of atelectasis. They also demonstrated that atelectasis is reversed only partially by lung inflation, and may persist into the postoperative period for more than 24 h.

The reduction in functional residual capacity associated with atelectasis is probably a result of changes in chest wall muscle tone and in thoracoabdominal blood volume [10]. If atelectasis is the cause of the increased venous admixture, then hypoxic pulmonary vasoconstriction (HPV) should compensate by directing blood from atelectatic to well-ventilated regions. Studies in animals have established that volatile anaesthetics abolish HPV. However, so far as patients are concerned, the addition of a volatile anaesthetic agent, even during one-lung anaesthesia, does not cause a decrease in oxygen saturation [5]. It has been known for more than 20 years that, even in non-anaesthetized man, HPV provides minimal compensation against the effects of atelectasis on venous admixture [14]. It appears from Eisenkraft's review [5] that the abolition of HPV by volatile anaesthetics is not an important cause of oxygen desaturation in man.

There can be no doubt that the pulse oximeter is a remarkable advance in respiratory monitoring which may reduce both anaesthetic morbidity and the costs of malpractice insurance. The widespread availability of this instrument means that clinicians can respond immediately to a decrease in Sa_{O_2} by increasing ventilation, FI_{O_2} or both without worrying (or even knowing) about obscure causes of venous admixture. However, they should bear in mind that one important cause of a sudden decrease in Sa_{O_2} during anaesthesia is an abrupt decrease in cardiac output. This does not mean that we can ignore atelectasis, because its persistence into the postoperative period causes a background of hypoxia against which abnormalities of respiratory control may cause obstructive apnoea and profound hypoxia. The importance of upper airway obstruction in the postoperative period has been emphasized [9], and the mechanisms leading to postoperative hypoxaemia have been reviewed recently [11]. Nevertheless, Goodman and Dodds [6] complained that "despite the exciting research into sleep-disordered breathing and its obvious importance for anaesthetists, very few appear to be aware of the syndrome of sleep apnoea or of its importance".

There appears to be an interaction between the effects of sleep, opioid analgesia and the waning effects of surgery and anaesthesia which cause a disturbance in respiratory control. This causes obstructive sleep apnoea, which exacerbates the hypoxia produced by atelectasis. Catley and colleagues [4] showed that episodic postoperative hypoxia was rarely associated with a slow breathing rate, so that this is an unreliable diagnostic sign. More recently, Wheatley and colleagues showed that opioid analgesia using a patient-controlled analgesia system (PCAS) was less likely than extradural opioid administration to cause night-time hypoxia [17].

An important question is "Does hypoxaemia matter?". This depends upon the degree of hypoxia and the type of patient. In normal subjects in whom FI_{O_2} was reduced to give resting Sa_{O_2} values of 58–68% and exercise values of 50–58%, there was a decline in both visual and verbal long term memory [8]. This was greatest in subjects with vigorous ventilatory responses to hypoxia and may have been caused by the effect of hypocapnia in decreasing cerebral blood flow. Little information is available in patients, but it would seem important that patients with coronary or cerebrovascular disease should not be allowed to become hypoxic. Indeed, such patients should be selected for particularly careful postoperative monitoring and oxygen therapy, which may be required for several days. It should be noted that hypoxia during obstructive apnoea may occur whenever a patient who has received opioid drugs falls asleep, night or day.

There are exciting developments in the assessment of respiratory muscle function. Most anaesthetists concentrate their attention on the assessment of neuromuscular transmission, assuming the muscles are capable of contraction if suitably stimulated. However, respiratory muscle function (particularly the onset of fatigue) is poorly elucidated from muscular responses to train-of-four stimulation, no matter what muscle group is examined. Moxham [13] reviews some important techniques for demonstrating and treating muscle fatigue. A particularly important development is the observation that sepsis has profoundly deleterious effects on respiratory muscle function and this may explain many cases of respiratory failure seen in the Intensive Care Unit. Rochester and Esau [15] have outlined the effects of critical illness and infection on the respiratory muscles. Cardiogenic shock predisposes to diaphragmatic failure and sepsis presents an even greater threat to respiratory muscle contractility. Diaphragmatic weakness occurs in sepsis despite there being no loss of muscle mass. Sepsis causes a considerable increase in respiratory muscle blood flow and an increase in oxygen consumption by the diaphragm, out of proportion to load, which suggests that oxygenation and phosphorylation may be uncoupled. These observations will encourage more objective measurements of respiratory muscle function and metabolism in septic patients.

The factors which influence ARDS and intrapulmonary airway calibre are reviewed extensively in this issue. There has been an "explosion" of information on mediators and mechanisms in both of these areas, but little improvement in understanding. There have been two notable advances in our understanding of ARDS. First, there is a more realistic view of the incidence of this disorder. Second, there is a more standardized definition which uses an acute lung injury scoring system, associated clinical disorders and systemic organ functions.

An oft-quoted estimate from the U.S.A. would give an incidence of 150 cases of ARDS per annum in a district serving 250000 people! This is completely at odds with clinical experience in the U.K. Webster, Cohen and Nunn [16] found an annual incidence of 12/250000 people in the Yorkshire region and a prospective study in the Canary Islands reported 5–10 cases per 250000 patients. This suggests that ARDS may be a much rarer condition than was believed to be the case.

The acute lung injury scoring system is based on the chest radiograph, the hypoxaemia score, total respiratory compliance and the magnitude of positive end-expiratory pressure (PEEP). While the first two of these seem to be acceptable, measurements of total compliance do not take into account the patient with a low chest wall compliance, and the degree of PEEP applied to a patient is dependent upon both practice and prejudice in a particular unit. There is a trend towards the use of much lower PEEP because of the higher mortality associated with PEEP when applied at 15 cm H_2O [3].

The question of increased lung permeability to protein and other smaller molecular weight solutes in ARDS was discussed in a previous editorial [9]. Calandrino and colleagues [2] showed some elegant pictures of increased protein in the lung fields of ARDS patients studied with Positron Emission Tomography, and made the important point that increased protein leakage persisted for more than 1 week. A more recent study using ^{99m}Tc-DTPA rather than protein [1] showed that

ARDS patients had "leaky lungs" persisting for up to 30 days after admission. The increased protein leak through the alveolar capillary barrier denatures lung surfactant, and a normal colloid oncotic pressure gradient can no longer be maintained across the barrier. Lung surfactant replacement therapy is said to be effective in the treatment of neonatal RDS and may be therapeutic in ARDS [12].

J. G. Jones and C. J. Hull

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RESPIRATORY MECHANICS IN ANAESTHESIA

J. MILIC-EMILI, F. M. ROBATTO AND J. H. T. BATES

The present knowledge of respiratory mechanics in anaesthetized humans is astonishingly scanty. This probably reflects the notion that measurement of the mechanics of ventilation during anaesthesia is difficult to perform. In fact, in mechanically ventilated anaesthetized–paralysed humans, a detailed analysis of respiratory mechanics can be performed readily with simple and commonly available equipment, namely a pneumotachograph to measure flow ($\dot{V}$), an integrator to obtain volume changes (ΔV) from the flow signal, and a pressure transducer to measure the pressure at the airway opening (Pao) or, preferably, in the trachea (Ptr) some distance beyond the distal end of the tracheal tube [12, 33]. Several commercial ventilators allow direct measurement of these variables (e.g. Siemens 900C, Puritan-Bennett 7200). With this equipment it is possible to determine, non-invasively, the static and dynamic elastance of the total respiratory system, the flow-resistances of the total respiratory system, airways and thoracic tissues and intrinsic PEEP [11, 34]. By adding an oesophageal balloon catheter system, overall respiratory system mechanics data can be partitioned into lung and chest wall components. In fact, contrary to previous belief, the oesophageal balloon technique is valid in the supine position in both awake [6] and anaesthetized subjects [21].

The present review is not intended to provide a comprehensive account of the literature, but rather to focus on new methodological and conceptual advances which stem from recent studies of the mechanics of ventilation in anaesthetized–paralysed animals [35] and man [11]. Several earlier accounts of respiratory mechanics during anaesthesia [17, 32, 33] deal with aspects not considered in this article because of limitation of space.

KEY WORDS

Lung mechanics, general anaesthesia

FORCES INVOLVED IN BREATHING

Breathing movements require work involving several mechanisms: (1) elastic forces; (2) resistive forces resulting from flow of gas through the airways; (3) viscoelastic forces attributable to stress adaptation units within the thoracic tissues (lung and chest wall) [22]; (4) plastoelastic forces within the thoracic tissues which cause "quasi-static hysteresis", as reflected by differences in static elastic recoil pressure of the lung and chest wall between lung inflation and deflation [22]; (5) inertial forces which depend on the mass of gases and tissues; (6) gravitational forces that may be considered as part of inertial forces but in practice are included in the measurement of elastic forces; (7) compressibility of intrathoracic gas; and (8) distortion of the chest wall from its passive (relaxed) configuration [18].

Inertial forces are normally negligible [25], and the same is true for compressibility of gas [23]. Similarly, in normal subjects with relaxed respiratory muscles, the thoracoabdominal configuration during lung inflation and deflation is close to that obtaining under static conditions [1]. Accordingly, in anaesthetized–paralysed subjects the pressure losses resulting from distortion of the chest wall during lung inflation and deflation should be negligible.

Resistance

Theoretical estimation

Based on the above premises, the conventional equation for describing the relationship between the flow-resistance of the total respiratory system (Rrs) and flow at a fixed lung volume is given by [26]:

$$R\text{rs} = R\text{t} + K_1 + K_2\dot{V} \qquad (1)$$

where Rt is flow-resistance of thoracic tissues, and

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K_1 and K_2 are empirical constants which describe the relationship between airway resistance (Raw) and flow:

$$R\text{aw} = K_1 + K_2\dot{V} \qquad (2)$$

Equation (1) is the basis for one of the tenets of respiratory mechanics, namely that, at a given lung volume, Rrs should increase with $\dot{V}$. Another basic tenet is that, at a given flow, Rrs should decrease with increasing lung volume because of a decrease in both Raw [8] and Rt [20], the former reflecting airway dilatation while the latter results because the linear velocity of thoracic tissues decreases with increasing lung volume, and hence the flow-dependent pressure losses within the thoracic tissues are reduced.

Equation (1) assumes that the thoracic tissues exhibit ohmic (Newtonian) behaviour. However, recent studies in anaesthetized–paralysed animals [35] and man [11] have shown that this is not the case. Bates, Brown and Kochi [2] demonstrated that a spring-and-dashpot model explains adequately the viscoelastic behaviour of thoracic tissues. In its simplest form, this model consists of two compartments in parallel: a dashpot representing Raw and a Kelvin body (fig. 1). The latter consists of a spring representing the static elastance of the respiratory system (Est,rs) in parallel with a Maxwell body—that is, a spring (E_2) and a dashpot (R_2) arranged serially. E_2 and R_2 represent viscoelastic properties of the thoracic tissues (lung and chest wall), while Est,rs and Raw are standard elastic and resistive elements. According to this model, Rt measured during constant-flow inflation from relaxed FRC (see below) should increase with the duration of inspiration (TI) according to the following exponential function [11, 35]:

$$R\text{t} = R_2(1 - e^{-T\text{I}/\tau_2}) \qquad (3)$$

where τ_2 is the time constant of the viscoelastic component of the thoracic tissues ($\tau_2 = R_2/E_2$). This equation implies that Rt is not constant but increases with TI. At the onset of lung inflation, Rt is zero; at $T\text{I} > 3\tau_2$ it approximates to R_2.

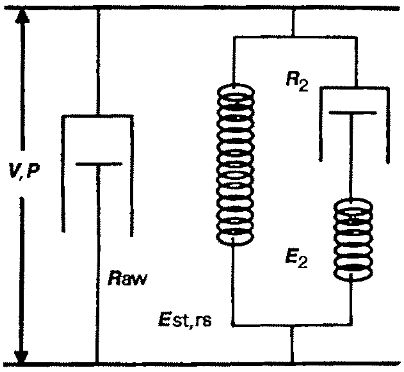

FIG. 1. Scheme of spring-and-dashpot model for interpretation of respiratory mechanics during flow interruption. The respiratory system consists of standard airway resistance (Raw) in parallel with a standard static elastance (Est,rs), and a series spring-and-dashpot body (E_2 and R_2, respectively) which represents the stress adaptation units. The distance between the two horizontal bars is the analogue of lung volume (V) and the tension between these bars is the analogue of pressure at the airway opening (P).

During constant-flow inflation there is a fixed relationship between inflation volume (ΔV) and TI:

$$\Delta V = \dot{V}T\text{I}$$

and accordingly:

$$T\text{I} = \Delta V/\dot{V}$$

If the latter is substituted into equation (3), it follows that:

$$R\text{t} = R_2(1 - e^{-\Delta V/\dot{V}\tau_2}) \qquad (4)$$

This equation implies that, during constant-flow inflation ($\dot{V} = \text{const}$) Rt should increase towards R_2 with inflation volume, and that, at fixed inflation volume ($\Delta V = \text{const}$), Rt should decrease progressively with increasing flow.

From equations (1), (3) and (4), it follows that, during constant-flow inflation:

$$R\text{rs} = R_2(1 - e^{-T\text{I}/\tau_2}) + K_1 + K_2\dot{V} \qquad (5)$$

or

$$R\text{rs} = R_2(1 - e^{-\Delta V/\dot{V}\tau_2}) + K_1 + K_2\dot{V} \qquad (6)$$

The significance of equations (3)–(6) will become apparent below.

Technique of rapid airway occlusion during constant-flow inflation

There are four approaches available for measuring flow-resistance: (1) the elastic subtraction method [29]; (2) the interrupter method [29]; (3) the forced oscillation method [15]; and (4) the plethysmographic method [14]. For obvious reasons, the last of these cannot be applied during anaesthesia. In the past, the forced oscillation technique could not be applied to anaesthetized subjects because of technical problems caused by the tracheal tube; however, a possible solution has been proposed recently [28]. The technique of rapid airway occlusion during constant-flow inflation is essentially a combination of two of the basic approaches for measuring flow-resistance described in 1927 by von Neergaard and Wirz [29]: the interrupter and the elastic subtraction methods. This approach was originally proposed by Rattenborg in 1956 [31]. A virtue of the technique is that flow-resistance can be measured at a fixed inflation flow but different inflation volumes, or at fixed inflation volume but different inflation flows. Furthermore, with this approach the measurements can be carried out with any preselected previous lung volume history.

Principles of measurement

Figure 2 illustrates a representative record obtained in an anaesthetized–paralysed human ventilated with a Siemens Servo 900C ventilator. Sudden end-inspiratory airway occlusion during constant-flow inflation resulted in an immediate decrease in *P*ao from a maximal value (*P*max) to P_1. Dividing $P\text{max}-P_1$ by the constant-flow immediately preceding the occlusion yields the interrupter resistance (*R*int). (Other symbols, such as *R*init [35] and *R*min [11] have also been used to describe the interrupter resistance.) Thus:

$$R\text{int} = (P\text{max}-P_1)/\dot{V} \tag{7}$$

Its significance has been clarified both in theory [5] and experimentally; essentially, it reflects airway resistance. Indeed, in elegant experiments in open-chested dogs in which alveolar pressure was measured directly using the alveolar capsule technique described by Fredberg and his colleagues [16], Bates' group [4] found that the immediate change in transpulmonary pressure following rapid airway occlusion during expiration was virtually identical to the pre-interruption pressure decrease between trachea and alveolus. Furthermore, in anaesthetized–paralysed man there is no appreciable change in oesophageal pressure immediately following airway occlusion [unpublished observations], indicating that $P\text{max}-P_1$ does not include pressure dissipations within the tissues of the chest wall. Therefore, in man, *R*int represents *R*aw, as originally proposed by von Neergaard and Wirz [29].

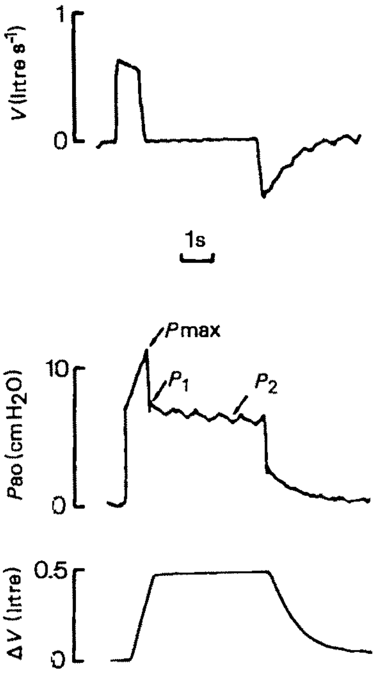

FIG. 2. Records of flow ($\dot{V}$), pressure at the airway opening (*P*ao), and changes in lung volume (Δ*V*) from an anaesthetized–paralysed subject which illustrate the technique of rapid airway occlusion during constant-flow inflation. After end-inspiratory airway occlusion there is an immediate decrease in pressure from *P*max to P_1, followed by a slow decay to a plateau value (P_2) that represents static elastic recoil pressure at end-inspiratory lung volume. The decrease in pressure from *P*max to P_1 includes resistive pressure attributable to the tracheal tube. For further explanations see text.

As shown in figure 2, the immediate decrease in *P*ao after occlusion is followed by a gradual decay in pressure from P_1 to an apparent plateau value (P_2) that represents the static end-inspiratory elastic recoil pressure of the respiratory system (*P*st,rs). This plateau pressure is usually reached in approximately 3 s. Dividing P_1-P_2 by the preceding flow gives an additional resistance (Δ*R*rs) [11]:

$$\Delta R\text{rs} = (P_1-P_2)/\dot{V} \tag{8}$$

The slow pressure decrease, P_1-P_2, reflects two phenomena: "pendelluft", which may be brought out by time constant inequalities within the lung or chest wall, and stress relaxation as a result of viscoelastic properties of the thoracic tissues. In normal humans, however, the time constant inequalities within the lung [30] and chest wall [1] appear to play a negligible role, and hence Δ*R*rs should essentially reflect the effective thoracic tissue resistance resulting from the viscoelastic behaviour of the thoracic tissues ($\Delta R\text{rs} \simeq R\text{t}$) [11, 35].

The significance of Δ*R*rs may be further interpreted as follows. When the model in figure

1 is elongated at constant speed (v), the charge of the spring E_2 increases with TI until, at $T\text{I} > 3\tau_2$, the speed in the dashpot R_2 approaches v, and hence the force exerted by the spring E_2 asymptotes to $R_2 \cdot v$. If a "flow interrupter" manoeuvre is performed by suddenly halting the relative movement of the two horizontal bars in figure 1, the length of spring E_2 will decay exponentially to its equilibrium length. In terms of this model, the post-interruption pressure decay ($P_1 - P_2$) is thus interpreted as the relaxation of the spring E_2, resulting in resistive energy dissipation in the dashpot R_2. The amount of relaxation of tension (stress relaxation) thus depends on the degree of stretch of spring E_2 at the time of interruption of flow. Clearly, ΔRrs is not a pure (Newtonian) resistance, and hence the term effective tissue resistance appears preferable.

Since $R\text{rs} = R\text{int} + \Delta R\text{rs} (= R\text{aw} + R\text{t})$, it follows from equations (7) and (8) that the total effective resistance of the respiratory system is given by:

$$R\text{rs} = (P\text{max} - P_2)/\dot{V} \qquad (9)$$

This equation can be viewed as an application of the elastic subtraction principle of von Neergaard and Wirz [29] because P_2 (which is subtracted from total pressure Pmax) is the static end-inspiratory elastic recoil pressure of the total respiratory system.

The technical aspects of the present technique have been discussed in detail elsewhere [3, 11]. Two points are of particular importance, namely the speed of valve occlusion and the effect of the compliance of the upper airways on the occlusion pressure. During anaesthesia the upper airways are bypassed by the tracheal tube, and hence artefacts related to the compliance of these structures are negligible. It should be noted also that determination of P_1 and P_2 is best made by curve fitting using a computer [3]. In assessment of Raw (and hence Rint), the nature of the gas breathed should be taken into account [33].

Measurements

Using the above technique, D'Angelo and his colleagues [11] studied the resistive properties of the ventilatory system in 16 anaesthetized–paralysed supine humans (enflurane–pancuronium; 50% nitrous oxide) undergoing ventilation of the lungs via a Siemens Servo 900C ventilator. All inflations started from relaxed FRC, and Rint was corrected for resistance of the tracheal tube, as described by Behrakis and co-workers [7]. Figure 3A depicts the average relationship between Rint and inflation volume during constant-flow inflation ($\dot{V} = 0.56$ litre s^{-1}) in the 16 subjects. In agreement with previous results on awake humans [8], Raw (as reflected by Rint) decreased slightly with increasing ΔV. The relationship between Rint and flow obtained in the 16 subjects at a fixed inflation volume ($\Delta V = 0.47$ litre) is depicted in figure 4A. Rint increased linearly with flow according to equation (2), the average (SD) values of K_1 and K_2 amounting, respectively, to 1.9 (0.5) cm H_2O litre^{-1} s and 0.5 (0.1) cm H_2O litre^{-2} s^2. These values are close to those observed in normal awake humans breathing through the mouth [26]. There are no previous studies of Rint in anaesthetized man, except for

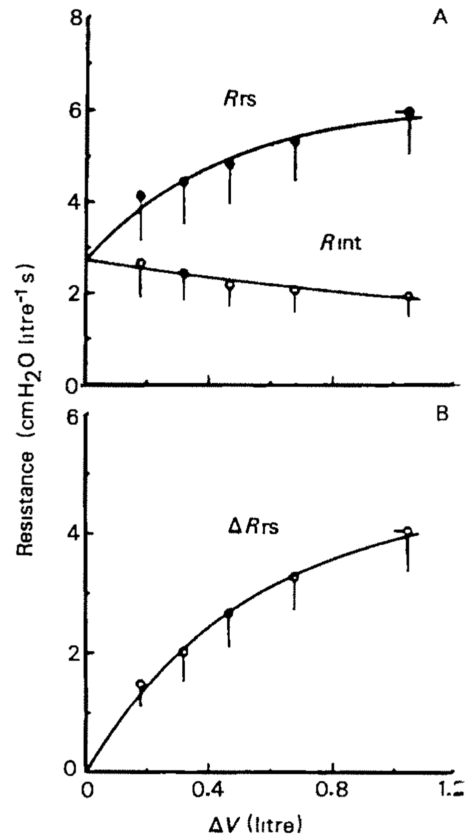

FIG. 3. A: Average relationship of Rrs and Rint with volume obtained at constant inflation flow (0 56 litre s^{-1}) in 16 anaesthetized–paralysed subjects. Bars: 1 SD. Rrs was obtained by adding ΔRrs (computed according to equation (4)) to Rint. B: Similar relationship in terms of ΔRrs ($\simeq R$t). Curves computed according to equation (4). (Reproduced with permission, from D'Angelo and colleagues [1].)

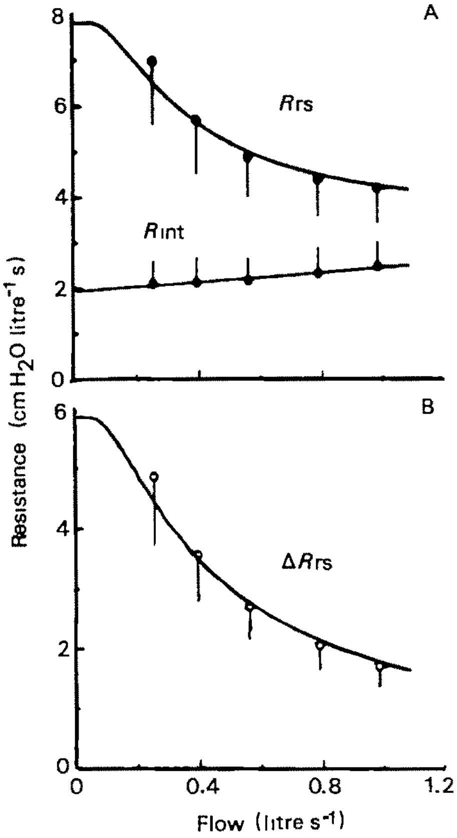

FIG. 4. A: Average relationship of *R*rs and *R*int with inflation flow obtained at constant inflation volume (0.47 litre) in same subjects as figure 3. Bars: 1 SD. *R*rs was obtained by adding Δ*R*rs (computed according to equation (4)) to *R*int. B: Similar relationship in terms of Δ*R*rs. Curves computed according to equation (4). (Reproduced with permission from D'Angelo and colleagues [11].)

that of Gottfried and colleagues [19], who made measurements during passive lung deflation in six anaesthetized subjects (halothane–nitrous oxide) both before and after paralysis. In this study, *R*int was essentially constant during most of lung deflation, amounting to 2.0 (0.8) cm H_2O litre^{-1} s during anaesthesia and 1.9 (0.6) cm H_2O litre^{-1} s during anaesthesia–paralysis. These values are similar to those in figure 3. It should be noted that, during lung deflation, volume (fig. 3A) and flow (fig. 4A) dependence of airway resistance tend to cancel out [36], and this may explain the constant values of *R*int found by Gottfried's group [19].

Figure 3B depicts the average relationship between Δ*R*rs and inflation volume during constant-flow inflation. The data fit equation (4) in all instances ($P < 0.001$), the average (SD) values of the coefficients R_2 and τ_2 amounting to 4.6 (0.8) cm H_2O litre^{-1} s and 1.0 (0.3) s. The increase in Δ*R*rs with inflation volume was greater than the concomitant reduction in *R*int (fig. 3); as a result, *R*rs increased markedly with inflation volume. Thus, contrary to previous belief, *R*rs does not decrease with increasing lung volume, but increases in line with our model predictions. It should be noted that equation (4) predicts that the volume-related increase in Δ*R*rs depends on the rate of constant-flow inflation: for any given ΔV, an increase in $\dot{V}$ will reduce the magnitude of Δ*R*rs because that volume will be reached with a shorter *T*I (equation (3)). This is shown in figure 4B, which illustrates the relationship of Δ*R*rs to flow at a fixed inflation volume: Δ*R*rs decreases with increasing flow according to equation (4) ($P < 0.001$). This is in contrast to equation (1), which indicates that *R*t (and hence Δ*R*rs) should have a fixed value. The decrease in Δ*R*rs with increasing $\dot{V}$ is greater than the concomitant increase in *R*int, and consequently *R*rs decreases markedly with increasing flow (fig. 4). The values of the constants R_2 and τ_2 in these isovolume experiments were similar to those found in the isoflow studies.

Don and Robson [12] made similar measurements of *R*rs in anaesthetized–paralysed man (thiopentone; 75 % nitrous oxide). Under normocapnic conditions, at constant inflation flow of 1 litre s^{-1} and ΔV of 0.7–1.0 litre, they found *R*rs values of 3.4 (1.4) cm H_2O litre^{-1} s. These are within the range of those found in the present study at corresponding flow (fig. 4A), but at a lower inflation volume (0.47 litre). Figures 3 and 4 show that *R*rs varies markedly according to the experimental conditions. Unless $\dot{V}$ and ΔV are standardized, comparisons of *R*rs appear to be meaningless. In contrast, the results of D'Angelo and colleagues [11] show that it is possible to describe adequately the resistive properties of the respiratory system in terms of *R*int, which represents airway resistance, and the constants R_2 and τ_2 which characterize the viscoelastic properties of the thoracic tissues. By measuring oesophageal pressure, it is possible to partition thoracic tissue resistance into lung and chest wall components. Preliminary results indicate that the lung tissues account for about 60 % of Δ*R*rs [D'Angelo and colleagues, unpublished observations].

Elastance

Theoretical estimation

The viscoelastic properties of the thoracic tissues not only contribute to Rrs, but also affect the elastance of the respiratory system. In fact, since P_1–P_2 may be interpreted as a charge on the spring E_2 (fig. 1), it follows that the effective elastance of the viscoelastic units within the thorax (Et) is given by:

$$Et = (P_1 - P_2)/\Delta V \quad (10)$$

Based on the model in figure 1, during constant-flow inflation from relaxed FRC, Et should decrease with inspiratory time according to the following function:

$$Et = (P_1 - P_2)/\Delta V = R_2(1 - e^{-T\text{I}/\tau_2})/T\text{I} \quad (11)$$

This equation shows that Et is time-dependent, as is Rt (equation (3)). In contrast to Rt, however, Et decreases progressively during lung inflation: at onset of inflation Et equals E_2, while at $T\text{I} = 3\tau_2$, Et equals 0.22 E_2.

During constant-flow inflation $T\text{I} = \Delta V/\dot{V}$, equation (11) can be transformed into:

$$Et = R_2(1 - e^{-\Delta V/\dot{V}\tau_2})\dot{V}/\Delta V \quad (12)$$

This equation shows that, at fixed inflation flow, Et should decrease progressively with increasing inflation volume. By contrast, at fixed inflation volume, Et should increase progressively with increasing flow, reflecting the shorter TI needed to reach that volume. TI-dependence of Et (equation (11)) implies TI-dependence of Ers. In fact, since standard elastance (Est,rs) and E_2 are arranged in parallel (fig. 1), the effective or *dynamic* elastance is the sum of Est,rs and Et. Time-dependence of Et, and hence of Ers, implies frequency-dependence of these variables. Otis and colleagues [30] have shown that frequency-dependence of Ers can be brought about by time-constant inequalities within the lung and (if any) chest wall. In normal humans, however, such inequalities are probably too small to play any significant role [30]. By contrast, the viscoelastic properties of the thoracic tissues play a significant role in determining dynamic Ers, as shown below.

When occlusion at end-inflation is maintained until a plateau in Pao is achieved (fig. 2), all elastic charge stored in the spring E_2 results in resistive energy dissipation in the dashpot E_2 (fig. 1). No external work is done. In contrast, if expiration does not entail an end-inspiratory hold, some of the stored elastic energy will be available for expiration, resulting in increased expiratory flow. In other words, the rate of lung emptying during passive lung deflation is greater the shorter the end-inspiratory hold, as described by Mortola, Magnante and Saetta [27].

Principles of measurement

Est,rs is obtained by dividing the difference between end-inspiratory and end-expiratory Pst,rs by ΔV. The end-expiratory Pst,rs is commonly defined as intrinsic PEEP (PEEPi) [34]. Thus:

$$Est,rs = (\text{end-inspiratory } Pst,rs - \text{PEEPi})/\Delta V \quad (13)$$

In anaesthetized–paralysed subjects with normal lungs, PEEPi is usually 0, provided that: (1) the expiratory duration is 3 s or more; (2) the size of the tracheal tube is not very small; and (3) the expiratory impedance offered by the ventilator is not too large. In patients with severe airway obstruction, PEEPi is almost invariably present [9]. If present, PEEPi has to be taken into account for correct measurement of Est,rs.

Dynamic Ers (Edyn,rs) is obtained by dividing the difference in Pao measured at points of zero flow by ΔV. In the subject in figure 2, who had no PEEPi, Edyn,rs is given by:

$$Edyn,rs = P_1/\Delta V \quad (14)$$

where P_1 is Pao measured at the point where inspiratory flow becomes 0.

The difference between Edyn,rs and Est,rs represents the tissue viscoelastic component of elastance, as defined by equation (10).

The technique of rapid airway occlusion during constant-flow inflation allows not only the measurement of static and dynamic Ers for a given volume change (equations (13) and (14)), but also determination of the static volume–pressure relationship of the total respiratory system, and definition of the function relating Et to inspiratory duration (equation (11)) or to inflation flow and volume (equation (12)). Using this technique it is also possible to determine the "quasi-static hysteresis" of the system without artefacts attributable to continuing gas exchange and shift of blood from the thorax [24] which are present when using the "super-syringe" method [10].

Measurements

The effects of anaesthesia on static elastance of the total respiratory system, lung and chest wall have been extensively studied. The results have been discussed in review articles [32, 33]. In man, *E*st,rs is usually found to increase after induction of anaesthesia; no further change occurs when either depth of anaesthesia is increased or muscle paralysis is added. The increase in *E*st,rs is caused primarily by an increase in static pulmonary elastance, probably reflecting an alteration in lung surfactant function. Dynamic *E*rs has also been measured during anaesthesia. The results, however, are difficult to interpret because *E*dyn,rs depends on the experimental conditions [11]. In 16 anaesthetized–paralysed subjects, *E*st,rs and *E*dyn,rs were measured at fixed inflation volume ($\Delta V = 0.47$ litre) but at different inflation flows. *E*st,rs was greater than normal but did not change with flow (fig. 5) [11]. In contrast, *E*dyn,rs increased with increasing flow, as predicted by equation (12). D'Angelo and colleagues also made similar measurements at fixed inflation flow (0.56 litre s^{-1}), but at different inflation volumes. In agreement with equation (12), under these conditions *E*dyn,rs decreased with increasing volume. It should be stressed that the apparent volume and flow-dependence of *R*dyn,rs merely reflects time-dependent behaviour of the viscoelastic compartment, as indicated by equation (11). The same is true in terms of the effective resistance offered by the thoracic tissues (equation (3)).

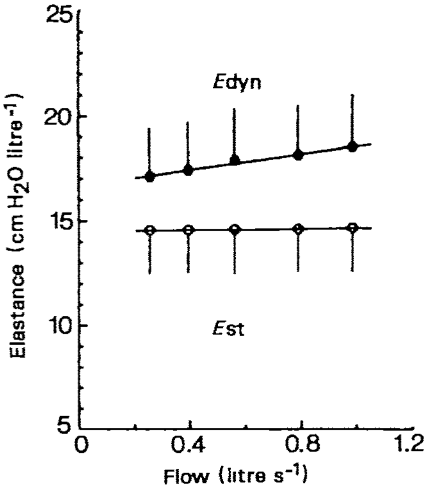

FIG. 5. Average relationship of static and dynamic elastance of the total respiratory system with flow obtained at constant inflation volume in same subjects as figure 4. Bars: 1 SD. (Reproduced with permission, from D'Angelo and colleagues [11].)

The above results indicate that *E*dyn,rs varies markedly with the experimental conditions. Unless $\dot{V}$ and ΔV are standardized, interpretation of *E*dyn,rs is difficult. In contrast, *E*st,rs together with the constants E_2 and τ_2 provide a full characterization of the elastic behaviour of the respiratory system. In the 16 subjects, the average (SD) values of these three variables were 14.5 (2.1) cm H_2O litre^{-1}, 4.5 (0.9) cm H_2O litre^{-1} and 1.0 (0.3) s, respectively.

Critique

The four-element model in figure 1 is not intended to be a complete and perfect representation of respiratory mechanics. Rather, it is what we consider to be a useful representation of the behaviour of the normal respiratory system during flow interruption. Obviously, one could invoke more viscoelastic elements in series and parallel, with a commensurate increase in the number of model parameters, in order to describe more accurately a particular set of data. However, D'Angelo and colleagues' results [11] closely fit the model predictions, indicating that such an analysis may be adequate. The same was true for experiments in anaesthetized-paralysed dogs [35]. Our model is superior to those described previously. For example, equation (1) predicts that *R*rs should increase with increasing flow, but this clearly is not the case (fig. 4). Our model predicts a non-linear relationship which is similar to observed data.

Our model contains no inertive elements such as are required to account for the behaviour of the respiratory system when very high frequency pressure oscillations are applied at the airway opening [13]. This is because the only evidence of inertia that can be detected during flow interruption is rapid and highly damped oscillation in *P*ao immediately after interruption. These oscillations invariably subside within 50 ms and can be discounted by back-extrapolation of the subsequent pressure signal.

Since, during lung inflation it is actually the charge on spring E_2 (fig. 1) that increases the impedance of the respiratory system, it could be argued that analysis should be limited to dynamic *E*rs and that assessment of effective tissue resistance (*R*t) is irrelevant. In theory, this argument has merit. In practice, however, all measurements of chest wall resistance, pulmonary flow resistance and Rrs axiomatically include a variable component reflecting viscoelastic behaviour of the tissues of the chest wall, lung, or both. Therefore, analysis in terms of Rt seems to be justified. It should be stressed, however, that assessment of Rt represents an "as if" analysis: it characterizes respiratory impedance "as if" the viscoelastic compartment behaved as a pure resistance. As if analyses are common in respiratory mechanics, as exemplified by the classic paper of Otis and colleagues [30] on the frequency-dependence of pulmonary compliance and resistance.

CONCLUSION

The technique of rapid airway occlusion during constant-flow inflation allows non-invasive determination of airway resistance, static compliance of the respiratory system, and thoracic tissue impedance. The effects of anaesthetic agents and of various drugs used during anaesthesia can thus be quantified in terms of both the standard mechanical properties of the respiratory system (Raw and Est,rs) and the impedance of the thoracic tissues. Determination of R_2, E_2 and τ_2 opens a new field for research. What are the effects of different anaesthetics on the viscoelastic properties of the thoracic tissues? What are the effects of age, lung disease, *etc*? These questions can now be answered quantitatively.

The technique of rapid airway occlusion during constant-flow inflation was first used by anaesthetists [12, 31]. Now they must apply it systematically in order to gain better insight to the effects of anaesthesia on respiratory mechanics.

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THE ROLE OF LUNG SURFACTANT

B. A. HILLS

Surfactant is essential for the wellbeing of the lung, a deficiency in quantity or composition causing atelectasis, alveolar flooding and generally compromising the spatial integrity of the mucosal surface needed for efficient gas exchange. The manner in which this delicate architecture can change has been well described in texts on the pathology of the respiratory distress syndrome (RDS) of the newborn [24, 76] and, more recently, in the adult form (ARDS) which is being diagnosed more frequently now that this specific disease entity has been recognized and better characterized clinically. The incidence of ARDS in the U.S.A. has been estimated [63] as 150000 cases per year, with a mean mortality rate of 50%. Surfactant is probably an important underlying factor in some cases of ventilator dependency, as the later discussion of its role in the work of breathing will imply.

There is also current research indicating that surfactant is present in its "active" state in many organs besides the lung and may provide the gastric mucosal barrier [50], the load-bearing lubricant in the joints [45], the release agent facilitating ventilation of the middle ear [12, 37] and the lubricant/release agent normally preventing premature rupture of the placental membrane [51]. A common metabolic pathway for the production of surfactant at different sites in the body could explain several interesting correlations between disease states—for example, why many patients with peptic ulcer also display impaired pulmonary function [56].

Despite the dominant role of surface factors in lung mechanics and alveolar flooding, surfactant is seldom mentioned in major reviews—especially of fluid balance in the lung [84, 85, 87]—probably because its inclusion invokes the relatively alien disciplines of physics and surface chemistry. However, it is surface activity which sets surfactants apart from other substances and so a little surface physics is essential for an in-depth understanding.

In this review we shall consider many basic aspects of the lung which, with few exceptions, have tended to be left in the "too-hard basket" for the past decade or two [42]. The more popular and pragmatic approach directed primarily to the problem of RDS has been to argue that, whatever its physical role, any deficiency in surfactant needs to be addressed by correction of the underlying metabolic problem or by supplementation with effective surfactant. Thus the major effort in the field today is either biochemical in nature or aimed at supplementation—either by promoting surfactant secretion with drugs such as ambroxol [60] or, more commonly, by administering exogenous surfactant to the neonate in various forms from various sources. The latest state of the art is contained in two volumes of collected papers published recently [20, 76]. The basic problem seems to be the compromise between the risk of transmitting pathogens and the loss in surface activity with processing of surfactant from natural sources. Although synthetic pathogen-free surfactant has so far defied dispersion in an aqueous medium while retaining surface activity of the "natural" material, that activity has been obtained in an ingenious formulation devised by Bangham and co-workers [7] in which the material is micronized into the air inspired by the patient. This has resulted in encouraging clinical results for premature babies [64], but such approaches return us to the basic question of what physical role surfactant is really playing at the alveolar surface.

KEY WORDS
Lung. surfactant.

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Surface activity

The molecules comprising any surface possess energy additional to that which they would possess if located in the bulk of that material—that is, they have additional (surface) energy simply by virtue of their location at an interface between two phases. This applies as much to solids as it does to liquids, although these do not have such obvious means of manifesting this energy as the surface tension which, for instance, enables a steel needle to be floated on water or a pondskater to stay dry. Many substances have the ability to change interfacial energies and the more effective of these are termed surfactants. They derive this ability (surface activity) from an unusual chemical composition in which their molecules are composed of two parts (moieties) of widely differing character. One part is polar and seeks water or hydrophilic surfaces, while the other is non-polar and seeks air or lipid, so they tend to locate at interfaces where both moieties can reside in compatible phases (fig. 1). A crude analogy is a football supporter who wears one team's colours on his left side and the other team's colours on his right side. Obviously, his location at the interface between the two groups of supporters would tend to minimize hostilities and reduce tension. Moreover, if his initial orientation were incorrect, he would soon be turned appropriately.

Needless to say, such amphipathic molecules have many desirable commercial roles which have led to the accumulation of knowledge in the physical sciences underlying a large industry producing surfactants from synthetic and natural sources. A good text on the basic physics and chemistry is that by Adamson [2].

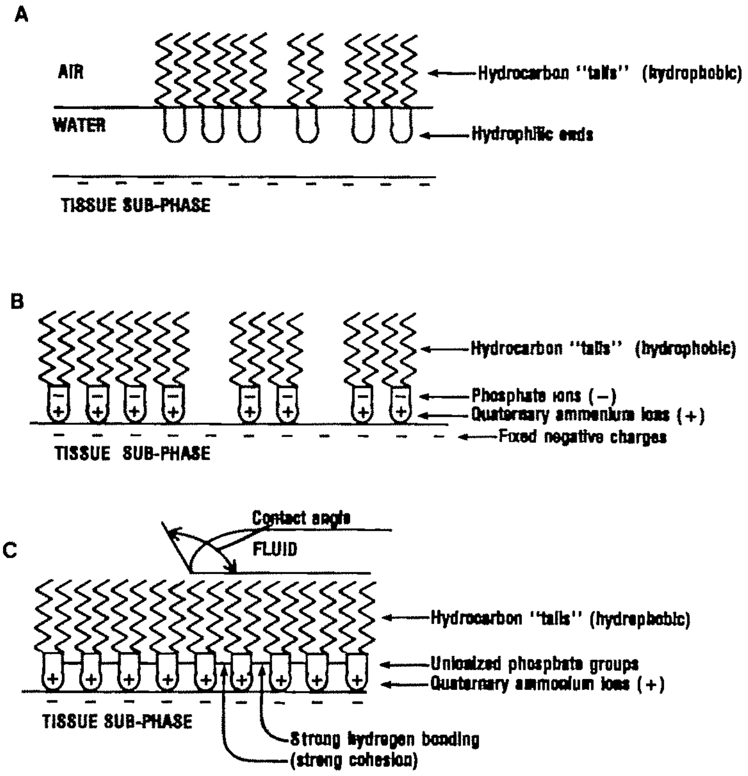
A
AIR
Hydrocarbon "tails" (hydrophobic)
WATER
Hydrophilic ends
TISSUE SUB-PHASE
B
Hydrocarbon "tails" (hydrophobic)
Phosphate ions (−)
Quaternary ammonium ions (+)
Fixed negative charges
TISSUE SUB-PHASE
C
Contact angle
FLUID
Hydrocarbon "tails" (hydrophobic)
Unionized phosphate groups
Quaternary ammonium ions (+)
TISSUE SUB-PHASE
Strong hydrogen bonding
(strong cohesion)

FIG. 1. Two basic modes of action of surfactant. A: At liquid–air interfaces where the polar ends of the molecules locate in the aqueous phase, orientating the molecule with its fatty acid chains in the air. B: At solid surfaces to which the polar ends can attach, orientating the fatty acid chains outwards to render the surface hydrophobic. C: How this adsorption can be enhanced in the case of surface-active phospholipid, by cations locating in the plane of the negative phosphate ions to pull them together, imparting cohesion, while the molecule is now effectively cationic, the terminal positive charge providing strong adsorption to a negatively charged mucosal surface.

What is surfactant?

In the lung the term "surfactant" is used to denote the mixture of phospholipid (67 %), neutral lipids (21 %), protein (8 %), carbohydrate (2 %) and other substances (2 %) secreted by the alveolar Type II cell, where it is produced as lamellar bodies. These represent a unique form of "packaging" which retains the extreme surface activity of the phospholipid in a state in which it is instantly available at a surface.

The characteristic feature of the lamellar body is its "Swiss-roll" appearance of tightly wound bilayers of phospholipid resembling myelin, which may have one or more foci (fig. 2). There is an enveloping membrane into which the inner lamellae never insert directly [27]. For a comprehensive text on lamellar bodies the reader is referred to the review by Stratton [86].

Lamellar bodies can be found in many other parts of the body, including the pleural cavity [89], parietal cells [89] and synovial fluid [45], while "whorls" highly reminiscent of lamellar bodies can be found in the brain, kidney and other organs [73], where their presence has hitherto been largely ignored, since some morphologists believe them to be the membranous remains of dead cells. They have even been found in material of vegetable origin, notably the banana [52].

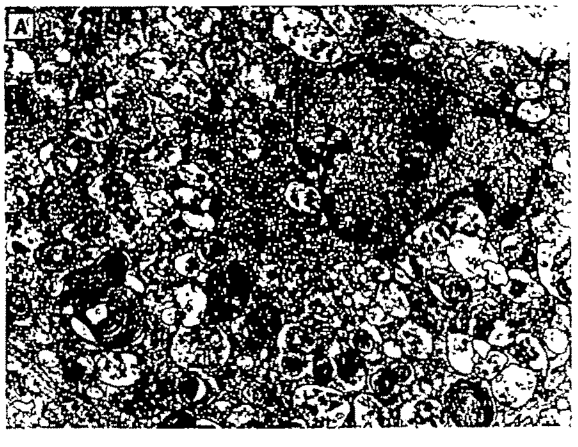

FIG. 2. Electronmicrographs showing lamellar bodies as tightly wound whorls of surface-active phospholipid. A: In lung; B: in parietal cells of the GI tract [42, 89]. ([89] reproduced by kind permission of Professor S. Ueda.)

Attempts to synthesize lamellar bodies have so far proven unsuccessful. Synthetic vesicles in such forms as liposomes [6] possess the low surface activity associated with "wet" surfactant, as opposed to the more potent "dry" form described by Morley and his colleagues [65]. For reasons yet to be resolved, the body has a remarkable ability to produce surfactant in an aqueous suspension possessing the surface activity of the dry form.

The surface-active ingredient is the phospholipid, especially the phosphatidylcholine (alias lecithin) which predominates in surfactant. The polar moiety is the choline group (fig. 3A), while both fatty acid chains of the non-polar moiety tend to be saturated and therefore straight, as depicted in the spatial diagram shown in figure 3B, C_{16} predominating and reaching 81 % in rat lung lamellar bodies [27]. The dipalmitoyl deriva-

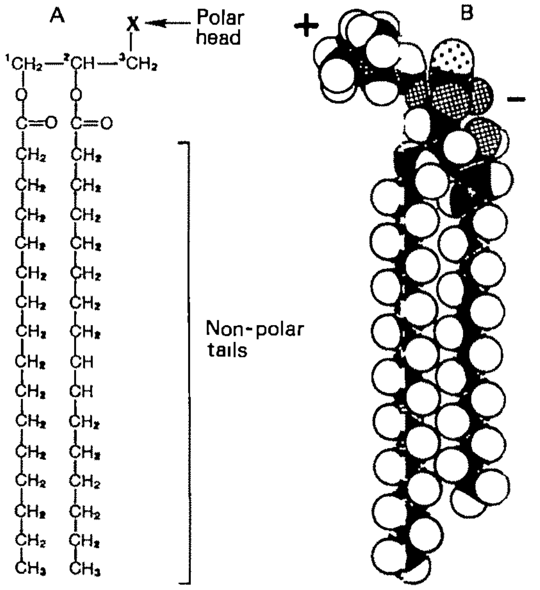

FIG. 3. Structure of the highly surface-active dipalmitoyl phosphatidylcholine (DPPC) as (A) the chemical formula and (B) the spatial arrangement. Note the two long straight fatty-acid chains.

tive is also the major phospholipid component of gastric juice, synovial fluid and amniotic fluid, the surface activity of which is manifest by the ease with which these fluids foam on shaking.

CONVENTIONAL THEORY

Assumptions

The roles traditionally attributed to surfactant in the lung are based upon two assumptions which are often not realized and are seldom, if ever, discussed. The first is that surfactant acts only at the air–liquid interface of a fluid lining to the alveolus, often termed an "aqueous hypophase" which, by the second assumption, is presumed to be continuous. Thus the conventional model of the alveolus is a one-sided bubble as depicted in figure 4. Any bubble has an inherent tendency to collapse until the internal exceeds the external pressure by a difference (ΔP) which can be quantified so conveniently by the Laplace equation, *viz.*:

$$\Delta P = 2\gamma/r \qquad (1)$$

where γ is the surface tension and r is the radius of curvature.

The simplicity of this expression in relating the surface tension (γ) to the mechanical properties has greatly enhanced the popularity of this model. Since alveolar volume represents about 60% of total lung volume and the radius of curvature is very small, giving large values for ΔP in equation (1), it is traditional to equate ΔP to the component of lung recoil contributed by the bubble lining (fig. 4).

Liquid filling

The recoil contributed by the bubble lining (ΔP in equation (1)) should be eliminated if the interface is eliminated by replacing the air in the alveolus by aqueous fluid. This was, indeed, found to be the case in the epochal experiment of von Neergard [66] whose data would indicate that the interfacial component contributed 75% of the recoil needed to return an excised lung to FRC, while later data would indicate a value closer to 87.5% [54]. Clearly, the interface makes the predominant contribution to lung recoil and, therefore, indicates a major role for surfactant.

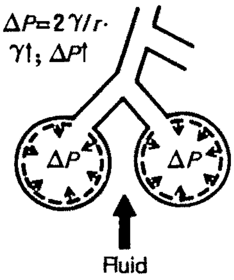

FIG. 4. The conventional "bubble" model of the alveolus, which assumes a continuous liquid lining. If the surface tension is too great, the alveoli may not only collapse, but also suck fluid into the intervening space as interstitial oedema.

Traditional explanation

The traditional explanation for the roles of surfactant is that, first, surfactant "makes breathing easy" by locating at the air–aqueous interface of the bubble lining, thus reducing surface tension (γ) and, hence, reducing the pressure (ΔP) needed to inflate the alveoli. Second, this reduction in ΔP reduces the negative pressure within the aqueous lining. This, in turn, reduces the pressure tending to cause oedema either by sucking more fluid directly into the alveolus or by causing adjacent alveoli to collapse, thus sucking more fluid into the intervening space as interstitial oedema.

In some elementary texts a third property is sometimes listed, in that a lower surface tension would reduce oedema by reducing the rise of fluid by capillarity in the "pores" or other channels through which interstitial fluid can flow to form alveolar oedema. However, this assumes that the pores only point upwards, in which case surfactant would have an adverse effect on retaining fluid in those pointing downwards [36].

Subsequent theory

If the conventional roles attributed to surfactant and the concomitant bubble model of the alveolus are essentially correct, then the following issues must be resolved:

(1) Since two interconnecting bubbles of different sizes (r values) will have different collapsing pressures if γ is the same in equation (1), further theory is needed to explain alveolar stability.

(2) Since the interface is the factor dominating lung recoil and since the large hysteresis in lung compliance is virtually eliminated by liquid filling [72], the above theory implies that much of the work of breathing is attributable to surfactant—a deduction difficult to accept teleologically.

(3) To what extent does surfactant need to reduce surface tension (γ in equation (1)) for ΔP to be compatible with both lung mechanics and fluid balance?

Reduction in surface tension

When substituting values in equation (1) for the radius of curvature of a *human* alveolus assumed to be a sphere ($r = 150$ µm), there is no difficulty in obtaining collapsing pressures (ΔP) of less than 5 mm Hg for γ values equal to the equilibrium surface tension of surfactant of 26 dyn cm^{-1} [42]. The equilibrium surface tension is the value reached when surfactant located on the liquid surface as displayed in figure 4 is allowed enough time to come to equilibrium with that suspended within the aqueous hypophase.

A problem arises when we consider the septal corners at which the curvature of any liquid lining is much greater. The radius of curvature is probably no more than 10 µm [53]; this value substituted for r in equation (1) would give a collapsing pressure, sucking fluid into the corner, of at least 25 mm Hg. This is physiologically improbable because interstitial pressure would need to be even more subatmospheric (< -25 mm Hg) to prevent alveolar flooding. No oncotic pressure can be invoked to assist homeostasis if alveolar oedema and interstitial fluid have the same composition [91, 92].

It has been argued that fluid would accumulate only until the septal corner is filled to a degree which allows the meniscus to follow the overall contour of the alveolar wall. The radius of curvature is then much larger and ΔP becomes more acceptable physiologically.

Small mammals

Shift of the lining liquid into septal corners has been the subject of several mathematical analyses, assuming a perfectly wettable epithelium [96], while the dynamic nature of the alveolar surface is almost invariably ignored. Red cells can be seen in all reflection electron microscopy scans, bulging their way through capillaries where they can switch a surface from concave to convex and *vice versa* very rapidly, as indicated by the estimate [77] that blood is retained in the gas-exchange zone of the lung for only 0.75 s.

"Rounding off the corners" by fluid shift can accommodate an equilibrium surface tension for the larger alveoli of larger mammals. However, for mammals such as the bat and the shrew where $r = 10$–15 µm, ΔP is again approximately -25 mm Hg [36, 42] even if the alveolus is assumed to be spherical. Hence we are forced to one of two conclusions: either the surface tension is much lower than the equilibrium value (less than 5 dyn cm^{-1}), or the whole concept of a continuous liquid ("bubble") lining is invalid.

Surface tension "near-zero" or not?

The foregoing arguments raise the obvious question of the capability of lung surfactant to reduce the surface tension of water to "near-zero" (< 5 dyn cm^{-1}). This leads us back to earlier work in which physiologists adopted the "tools" used by surface chemists to study the molecular dimensions and phase changes of various natural and synthetic surfactant monolayers. The classical apparatus is the Langmuir trough depicted in figure 5, in which a solution of surfactant in an immiscible solvent such as chloroform is allowed to spread over the surface of a pool of water. When the solvent evaporates, a surfactant monolayer remains. The surface tension is then measured as the vertical "pull" on a platinum flag dipping into the pool (Wilhelmy method) or the horizontal pull on a floating dam (Langmuir method) as a barrier is advanced to reduce the area of the monolayer. By compressing the pool area by 5:1 or more, surface chemists have been able to study the very interesting phase changes which monolayers can undergo, ranging from the equivalent of "gaseous" to "solid" phases as the molecules become close packed. In the solid state they can also undergo melting when the temperature is increased as demonstrated by a dramatic increase in surface tension.

When the same techniques are used to study lung surfactant as a monolayer recruited to the surface by lung rinsing or as a monolayer of a very pure ($> 99\%$) sample of the most active ingredient, Lα-dipalmitoyl phosphatidylcholine (DPPC), it is possible to obtain a near zero reading on the Wilhelmy flag (fig. 6). These findings are much quoted in support of the conventional theory whereby surfactant acts simply as a detergent in reducing the surface tension of the "bubble" lining on which it is predicated, and in support of much theory of fluid balance in the lung [84, 85], including the concept of negative interstitial pressure [31].

Artefact or not?

The results shown in figure 6 are easy to reproduce [42], but give several reasons for concern. The first is why the proponents of the conventional theory should emphasize only the least (near-zero) value obtained at maximal

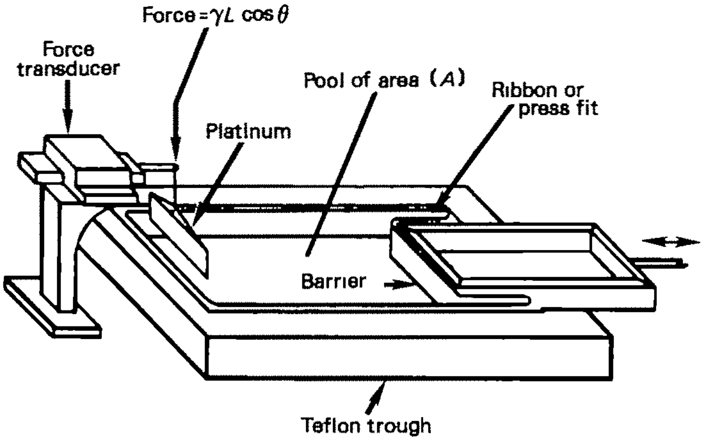

FIG. 5. A Langmuir trough as used widely by physicists and physical chemists to study molecular dimensions and the interesting phase changes of surfactant monolayers which occur when the surface area undergoes large changes. In respiratory studies a platinum plate is immersed in the pool—as shown—to monitor surface tension by the Wilhelmy method but, all too often, the contact angle (θ) is ignored in relating the surface tension (γ) to the recorded force—and an artefactually smaller value is obtained. L = Wetted perimeter.

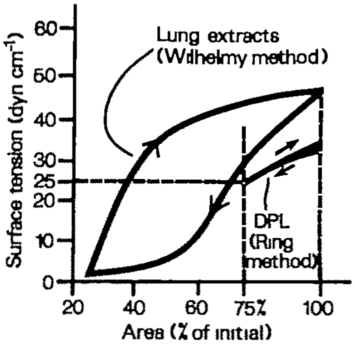

FIG. 6. Relationship between the apparent surface tension recorded by the Wilhelmy method (fig. 5) when the surface area of a monolayer of lung surfactant or synthetic DPPC is cycled over an area change traditionally used by physicists to study phase changes on the Langmuir trough. Note the near-zero value at maximum compression. Also shown is the true surface tension measured by a method (ring method) (DPL = dipalmitoyl lecithin) independent of contact angle when the same monolayers are cycled over the maximum area changes which can be justified by morphological studies of ventilatory movement. Note the much greater value for minimum surface tension—a value coinciding with the equilibrium surface tension.

compression and not the greatest or even the mean value, since the surface tension increases rapidly upon expansion of the film. It would seem necessary by the conventional model to postulate a Maxwell's Demon which could turn off the tap to any adverse flow of fluid across the alveolar membrane when the collapsing pressure (ΔP in equation (1)) increases to unacceptable values during inspiration.

The second problem concerns a contact-angle (θ) on the platinum plate (fig. 7) which, if greater than 0 and ignored, would give artefactually low values for surface tension (γ), the Wilhelmy method being used in the vast majority of physiological studies. The argument in favour of this method [69] is that the plate is cleaned until θ is zero. However, that is *before* the run and *before* the plate comes into contact with surfactant which is then adsorbed to the plate, rendering it hydrophobic with a contact angle which varies as the meniscus runs up and down the plate, but can reach 70° [42].

Simulation of ventilation

The second major objection to the recording of near-zero surface tension vital to conventional theory concerns the area change needed to reach those low values. It is quite acceptable to use 5:1 area changes to study molecular dimensions as the early surface chemists did, but not acceptable to claim that this degree of movement is in any way related to respiratory movement. In this regard, it is very difficult to justify an area change of more than 25% [71] and from morphological studies [26, 29] 6% would seem more appropriate [42]. Some morphologists [95] favour a concertina model in which alveolar volume can change with no change of area. Even with a 25% area change

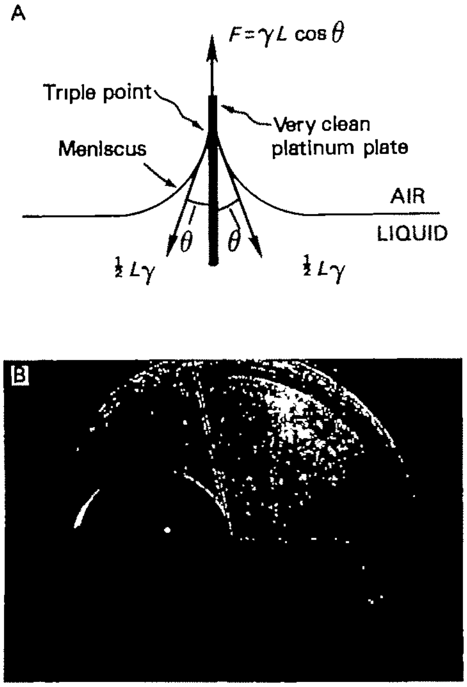

FIG. 7. A: Depicting the role of any contact angle (θ) in reducing the vertical pull on a platinum flag used to measure surface tension and how the value would be zero when $\theta = 90°$—that is, the pull is horizontal. B: Showing a contact approaching 90° on a platinum flag *after* it was used to obtain the type of loop shown in figure 6. Before use with surfactant, it was perfectly wettable ($\theta = 0$).

and permitting contact-angle artefact, the Wilhelmy estimate of surface tension cannot be reduced to less than 18 dyn cm^{-1} [9] at 37 °C.

The pulsating bubble

For numerous reasons, including those discussed above, some research workers have switched to a simple method [21] for measuring surface tension (γ) based upon equation (1). They measure ΔP for a very small bubble formed in lung fluid as its volume is changed hydraulically. This is based on a test designed for pure liquids in which renewal of the surface minimizes the effect of any contamination, but was considered unsuitable for those of low surface tension [5], presumably because the surface energy was now much less than the kinetic energy of the system. This was the reason why a much earlier dynamic method—the ripple method [42]—could not be used at low surface tension.

Thus inertial factors could be responsible for the low values of surface tension (2 dyn cm^{-1}) recorded for maximal compression of 2:1 at normal ventilatory frequency. This criticism tends to be supported by the fact that, as amplitude and frequency—and hence inertia—are increased, not only is the minimum surface tension decreased at maximum compression, but the maximum surface tension for zero compression is *increased*, reaching 30 dyn cm^{-1} [1]. This may seem to be belabouring physical measurements which one might expect to be simple but, in reality, it is very difficult to measure low surface tensions and yet the result is vital to the selection of a model for the alveolus and the concomitant role of surfactant.

Physiological conditions

If one returns to the quasi-static well defined conditions afforded by the Langmuir trough (fig. 5) and measures surface tension by the du Noüy ring [8] or the Langmuir [40] methods which avoid contact-angle artefact, there are two clear differences compared with previous studies. First, the hysteresis loops in $\gamma:A$ under simultaneously simulated physiological conditions are much thinner as seen in figure 6, with major implications to the work of breathing. This is important because the area of the loop has the dimensions of work and its magnitude represents the interfacial contribution to the work of breathing. This is generally considered to be a major portion of the elastic component of the work of breathing because compliance (pressure : volume) hysteresis is virtually eliminated upon liquid filling [72] which would eliminate any liquid–air interface and, hence, the bubble lining. Teleologically, it has never made sense that the body would locate a surfactant at the alveolar surface which would make it work harder—and much harder, according to the magnitude of the $\gamma:A$ put forward by proponents of the bubble model (fig. 6).

This leads to the second major difference, in that measurements made over physiological area changes do not reach a near-zero value for surface tension at any point in the cycle and therefore cast serious doubt upon the validity of alveolar models based upon a continuous liquid lining with surfactant simply acting at a liquid–air interface. However, before seeking alternative models it is necessary to consider how the bubble model can explain the vital question of alveolar stability.

Alveolar stability

The ability of the lung to maintain the spatial integrity of a gas exchange surface the size of a tennis court with an *interconnected* volume of 2–3 litre, and a constantly changing volume at that, is an amazing feat of design. This remarkable feature has not received the credit it deserves because, outwardly, it resembles a foam, which we all know can be stable. In a foam, however, two adjacent bubbles of different sizes with the same surface tension can co-exist because each will compress the air within until they reach different pressures in accordance with equation (1). If they are now interconnected, then the smaller bubble with the larger collapsing pressure (ΔP) will collapse ($r_1 \downarrow$), forcing gas into the larger bubble ($r_2 \uparrow$). What exacerbates this inherent instability of two interconnected bubbles is the manner in which the pressure difference between the bubbles, $2\gamma(1/r_1 - 1/r_2)$, increases as the change occurs, thus accelerating the process until there is total collapse of the smaller bubble.

Proponents of the bubble model [15] suggest that, upon inspiration, the surface tension of the larger bubble will increase less than that of the smaller bubble as determined by the $\gamma{:}A$ relationship depicted in figure 6, until γ/r is the same for both and so there is stability. This means, in effect, that they are postulating different surface tensions in adjacent alveoli.

This assumption has been criticized on several accounts [42]. First, whereas it is plausible to accept the above explanation for a few breaths, it is difficult to see why surfactant is not derecruited into the aqueous hypophase faster from the monolayer with the lower surface tension than from the other, thus bringing the surface tensions closer together and so re-introducing the question of instability, but over a longer time frame. Derecruitment of surfactant from monolayers of natural lung surfactant has been shown to be quite a rapid process, to the extent that those workers [33] have referred to the process as "film collapse". Cholesterol and proteins have been implicated in facilitating transfer of the surface-active DPPC to and from the monolayer [42].

The second objection to conventional theories of alveolar stability arises from the difficulty in perceiving different surface tensions in adjacent alveoli. If they postulate continuity of the liquid lining *within* each alveolus, then surely that continuity must extend *between* alveoli, especially when they are interconnected by terminal airways and even the pores of Kohn within the septal walls. One is forced to the conclusion that either the instability issue is not a problem because we are not dealing with bubbles in the first place, as discussed later, or the surface viscosity does not permit the flow of surfactant from one alveolus to another.

In defence of the continuous liquid lining one can invoke the "interdependence" concept of Mead, Takashima and Leith [62] by which alveoli can derive some degree of mechanical stability from their back-to-back or "honeycomb" configuration; the role of connective tissue has been discussed elsewhere [94]. However, if such factors were important, then atelectasis should never occur and certainly not so readily as we see when the surfactant system is compromised [67]. This returns us to the search for alveolar models with a large degree of *independence*.

Following current thinking [57] that lamellar bodies "pop to the surface" of the aqueous hypophase, contributing their surfactant to the monolayer, it would be necessary for them to pop to the surface faster in the smaller than in the larger alveoli in order to maintain the difference in surface tension needed to maintain (γ/r) the same in both adjacent bubbles. No such differential rate of recruitment has yet been demonstrated. Even if it were, then we are faced with the earlier question of why the monolayer would not flow from one alveolus to the next.

Surfactant monolayer: solid or not?

This question is not only relevant to the "shell" model of alveolar stability, but merges with the earlier issue vital to the bubble model of whether surface tension is near-zero or not. The surface tension of lung surfactant, or its most active ingredient (DPPC), can be reduced to give a reading of near-zero on the Wilhelmy balance only if the monolayer is transformed into the solid state. The vital question, therefore, is if surfactant on the liquid lining *is* in the solid state, still assuming there to be a liquid lining.

There is no doubt that pure DPPC at an aqueous surface *can* be packed into a condensed monolayer—that is, the surface equivalent of a solid state—with a melting point of 41 °C [7]. Unfortunately, the situation is more complex, for several reasons. First, surfactant produced in the lamellar body is a mixture of phospholipids which, at a surface, acts like solids in forming eutectic mixtures, thus reducing the melting point—in this case to 30–35 °C. It is therefore necessary to postulate that area changes associated with respiratory movement can "refine" surfactant by derecruiting impurities until the melting point exceeds 37 °C [23, 93]. This argument is difficult to prove *in vivo* and runs into problems when considering the following issue.

Surfactant: solid or not?

The role of surfactant and the model to adopt for the alveolus are closely interrelated and so it is the combination of bubble model and surfactant acting at a continuous liquid–air interface which really needs validation. This is ultimately dependent upon the surfactant on the liquid lining being in the solid phase, since this is the only state in which surface tension can reach near-zero values and surfactant can no longer flow between adjacent alveoli to re-introduce alveolar instability, for reasons discussed above. Solid surfactant could also form a rigid shell with each alveolus to stabilize it mechanically—as proposed by Bangham, Morley and Phillips [7] and Morley [64]. The vital question is whether any surfactant at the air interface of the assumed liquid lining is at a temperature greater or less than its solid melting point (transition temperature).

A monolayer of pure DPPC on water has a melting point of 41 °C [23] which is greater than the normal human body temperature of 37 °C. However, the phospholipid mixture as secreted by the alveolar Type II cell has a transition temperature of about 30 °C, so that it would require extensive refinement in order to reach a melting point in excess of 37 °C [23, 93]. It is a moot point if area changes associated with normal ventilation can achieve such fast and efficient "squeezing out" of other phospholipids from the monolayer, however rapidly new packages of phospholipids may be released as more lamellar bodies "pop to the surface" [42]. This writer is sceptical that the solid state could be formed because, even starting with pure DPPC on the pool of a Langmuir trough (fig. 5), it requires a compression far in excess of any predicted in the lung in order to attain a condensed monolayer (solid film).

Even if the film were 100 % refined to a melting point of 41 °C, the mechanical properties of lungs show a sharp transition upon warming within the range 42–47 °C [55]—appreciably greater than predicted by melting of a floating monolayer of solid surfactant [42]. There is the further point that mammals other than man but with essentially the same surfactant (e.g. sheep) can respire without overt lung changes with a core temperature up to 45 °C, while 43 °C is lethal to man [79]. Hence it is very difficult to envisage surfactant on the aqueous lining in the solid state needed to satisfy the bubble model

Other aspects

When a monolayer of natural surfactant recruited from lung rinsings is compressed several fold on a Langmuir trough, the apparent surface tension (Wilhelmy reading) is reduced to near-zero. However, if that compression is maintained, the surface tension increases rapidly, reaching an equilibrium value of 22–25 dyn cm^{-1} within approximately 1 min. This very labile situation is in stark contrast to that in the excised lung, which should correspond to maximum film compression where volume remains almost constant at zero retraction pressure for a matter of hours. Moreover, temperature has negligible effect upon the rate of stress adaptation of dog [46] and cat lungs over the range 22–47 °C—in sharp contrast to the effect of temperature upon monolayers of surfactant and their rate of collapse [33].

Horie and Hildebrandt [54] and Hoppin and Hildebrandt [53] have gone on to calculate surface tension:area ($\gamma:A$) relationships from pressure–volume curves, making certain geometric assumptions. These plots all show $\gamma:A$ relationships totally unlike any obtained with surfactant on the Langmuir trough, an example being a greater rate of increase of surface tension at greater film expansion [53]. These and other [42] discrepancies, when considered in conjunction with the very questionable basis for surfactant monolayers existing in the solid state which is a necessary condition for the bubble model, have led some to seek alternative approaches to the combination of alveolar model and role for surfactant.

ALTERNATIVE APPROACHES

The totally "dry" model

Teleologically, it does not make sense to cover the gas exchange surface of the lung with a liquid layer which simply adds another resistance to the blood–air barrier [34]. Thus Colacicco [16] has proposed that the alveolar surface is normally dry and that surfactant is only introduced in response to stimuli which cause flooding. This is an interesting notion, but can only be accepted if the numerous morphological studies showing fluid in the alveolus under normal physiological conditions are dismissed as artefact. It is easy to

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introduce artefact in electronmicroscopy and especially in lung tissue, but almost the only state of the alveolus not demonstrated so far has been one which is totally devoid of surface fluid.

Basic assumptions

The shortcomings expressed above in the argument for the combination of bubble model and theory of surfactant acting simply by reducing surface tension of a liquid lining have led this writer to return to the two basic assumptions on which it was predicted. Is there really a continuous liquid lining and does surfactant function only by locating at its interface with air?

The first question is important not only because surfactant cannot act at a liquid–air interface if there is no liquid present to provide an aqueous hypophase, but also because a discontinuous liquid lining no longer represents a bubble. Hence there is no longer a tendency for self accelerating collapse and the associated problem of instability which requires so much theory by the conventional approach.

The second question has never been seriously considered by most in the field, who are unaware that surfactants can act at solid surfaces as well as liquid–air interfaces. This possibility was recognized in an earlier experiment in which the platinum flag of the Wilhelmy balance was coated with pulmonary epithelium [46] to try to eliminate the contact angle. In the presence of surfactant, the surface became hydrophobic with a contact angle of approximately 70°. This indicated direct adsorption of surfactant on to epithelium and was compatible with the earlier studies of Cavagna and colleagues [14], who found that surface activity was associated more with the cellular content of lung rinsings than the liquid phase, although those authors offered no explanation for their findings.

Water repellency

The foregoing evidence leads to the obvious question of what functional advantage could be derived by direct adsorption of surfactant to the alveolar surface. In the physical sciences, adsorbed layers of synthetic cationic surfactants are used widely to impart many desirable properties, including lubrication, release, water repellency, bacterostatic action and to act as fabric softeners [2, 87]. In the case of the last of these, an adsorbed monolayer of surfactant prevents the microfilaments of a woven fabric from clumping and generally preserves spatial integrity—a highly desirable property for a structure such as the lung [34]. DPPC is effectively a cationic surfactant when the phosphate group is neutralized by a cation such as Na^+ (fig. 1c).

Another particularly relevant property of surfactants adsorbed to solid surfaces is water repellency. This could be highly relevant to the lung for two reasons. First, a surfactant can act in the true sense of a water repellent by acting at the ends of the pores or other channels through which fluid can exude onto the alveolar surface, to prevent flow. The capability of DPPC to impart this property even to such open structures as cotton, withstanding water penetration pressures well in excess of pulmonary arterial pressure, has been demonstrated clearly [35].

The second role of directly adsorbed surfactant is to render the epithelial surface hydrophobic and thus break up any fluid layer into a discontinuous liquid lining. This discontinuity is supported by experiments in which droplets of saline [43] or fluorocarbon [82] show a remarkable "duplicity" of behaviour upon impinging on the surface—either merging instantly or standing proud. The degree of hydrophobicity which can be imparted is difficult to assess in the lung itself, but it has been argued [17] that the amnionic mucosa comes into contact with fetal aspirates containing surfactant in its natural state. Even though the concentration is no more than 10% [10] of what it is in the fetal lung, the chorioamnionic sac can display a remarkable degree of hydrophobicity as compared with Teflon (fig. 8). It is tempting to speculate from such photographs that the neonatal

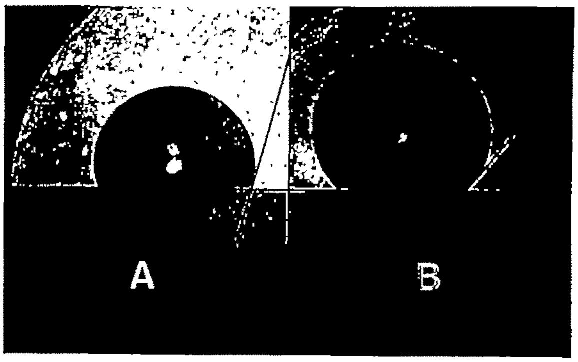

FIG. 8. Maximum contact angles recorded when a droplet of saline is placed on Teflon (A) and the epithelial surface of the amnion (B) which has been in contact with surfactant aspirated from fetal lungs.

lungs are effectively Teflon-lined, such hydrophobic surfaces causing fluid to exit in any way possible during the first few breaths.

A new model

The foregoing arguments have led to the model proposed in figure 9A and compared with the bubble model in figure 9B. The process suggested is direct adsorption of surfactant to the epithelial surface which is then hydrophobic, breaking up any fluid over the gas exchange area and causing it to collect as "pools" in the septal corners and "pits" as observed in electronmicrographs [25, 26, 28, 94] in which great care was taken not to disturb the alveolar surface by using vascular fixation. Tension is then applied to the epithelial membrane by the fluid in the pool gripping it at the edge and gathering it inwards as the observed "pleats", until the desired tension is attained. These pleats in the pools resemble soaking wrinkles and contrast markedly with the smooth contour of the epithelium between pools, indicating that those areas are effectively dry. This view [42] is supported by the findings upon liquid filling [26], when the whole epithelial surface becomes wrinkled and pleated.

The change in mechanical properties upon liquid filling can be attributed to the elimination of the pits and pools and, hence, the edges at which the liquid–air interface can grip the dry epithelium and so tension it. There would thus be a very good case for the way in which the surface tension tends to an equilibrium value of 25–26 dyn cm^{-1}—an equilibration which the proteins seem designed to accelerate. Thus the hypophase, where it exists in the pits and pools, could be designed to maintain constant surface tension and, hence, constant wall tension—quite the reverse of the role needed by conventional theory to provide stability between a chain of interconnected bubbles.

Electron microscopy

The reader may ask why the whole issue of the alveolar model, and hence the role of surfactant, cannot be settled by a few electronmicrographs

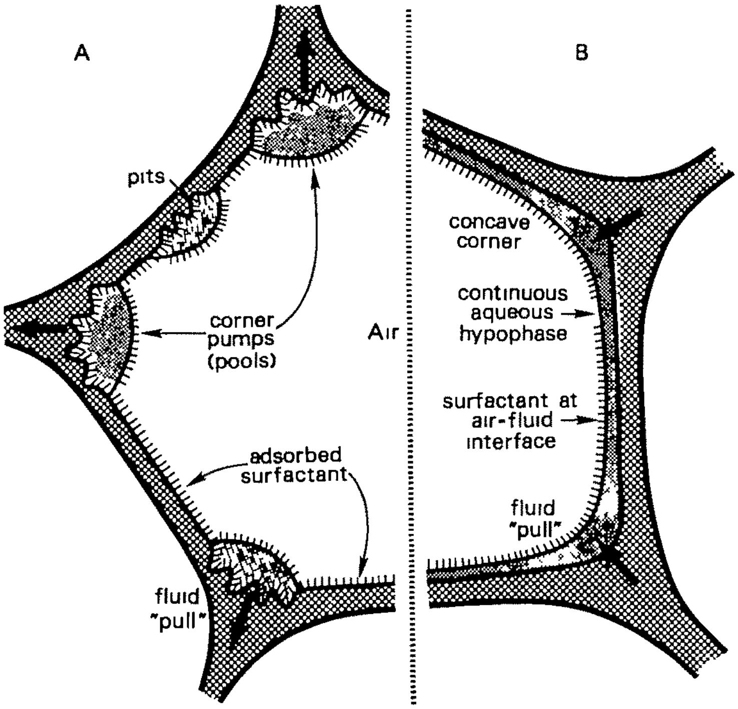

FIG. 9. A: The "discontinuous" model of the alveolus with fluid confined to pools and pits from which it is able to tension the dry patches of the wall by pulling in excess epithelial membrane as pleats. The gas transfer surface is kept essentially dry by water repellency induced by a monolayer of surfactant adsorbed directly onto the epithelial surface. The pools can assume a convex profile to act as corner pumps [35] for returning fluid to the interstitium. If flooding continues, the pools will link up to form the bubble model (B), but as a *pathological* and not the normal physiological state.

which show whether or not there is a continuous liquid lining with surfactant located at its surface. Phospholipid is highly osmiophilic [30] and so there should be a simple answer. Unfortunately, electronmicrographs can be produced to support almost any theory except a totally dry alveolus. In normal lung tissue it is also difficult to demonstrate a continuous liquid lining with a supernatant surfactant layer, as was of concern to Pattle [70], who was an advocate of the bubble model. The argument then becomes one of whether surfaces which are apparently free of fluid are really dry or have a liquid layer a few molecules in thickness which are easily rewetted as fluid is moved around by respiratory movements and by blood cells bulging their way through the capillaries just beneath the alveolar epithelium. This question is difficult to answer in morphological studies although the "droplet" experiments described above would tend to suggest that there are distinct dry areas and wet areas, corresponding to the pits and pools described in the last section. One of the problems is the almost universal use of aldehydes as fixatives, since these are known [90] to "destroy hydrophobic surfaces" and could thus produce electron microscopy scans favouring the bubble model. Even so, some [18, 58] show droplets standing proud on what, by conventional theory, should be wettable surfaces.

Tannic acid has been substituted for much of the glutaraldehyde, facilitating the production of a series of superb electronmicrographs by Ueda and his colleagues [88, and cited in [42]] which showed surfactant directly adsorbed to the epithelial membrane. This adsorbed phospholipid is either a monolayer (fig. 10A) or an oligolamellar layer (fig. 10B), but no fluid can be seen separating tissue from surfactant. Oligolamellar layers are also hydrophobic [45].

Critique of the water repellent model

Although recent electron microscopy would tend to support the water repellent model, it has been criticized for several reasons. First it is, as Brooks [13] has so aptly expressed it, "unthinkable" to most in the field that the alveolar surface is not totally "moistened". This is certainly true of airways, but the approximately 50 cell types capable of secreting and contributing to the mucous lining are proximal to the alveoli, the surface of which could therefore be quite different. A common criticism [11] of the water repellent model is why there should be a correlation between the clinical condition of patients with RDS and the ability of recovered surfactant to decrease the surface tension of water. The answer is that this ability would reflect surface activity in general and any deficiency would therefore indicate a similar deficiency in its capability to be adsorbed to epithelium. Another criticism raises the question of how surfactant could be replenished on a dry patch, but this is easily answered by its presence in the underlying interstitial fluid and its ability to move across dry surfaces by a process known as surface diffusion [42].

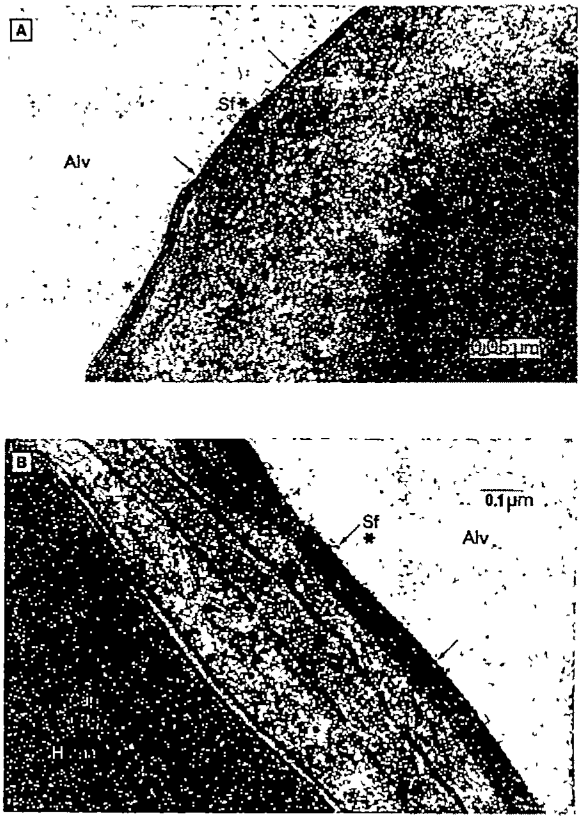

FIG. 10. Electronmicrographs of the alveolar surface showing the surfactant (sf) (A) as a monolayer directly adsorbed to the epithelial membrane [88] and (B) as an oligolamellar layer. In no case is there an indication of any liquid separating the surfactant from the epithelial membrane. (Reproduced by kind permission of Professor S. Ueda.)

FLUID BALANCE

The foregoing comparison of alveolar models has largely concerned the more mechanical aspects of alveolar function, but this leaves the vital question of fluid balance in which many reviews ignore surfactant despite a dominant role in alveolar flooding.

Conventional approaches

The success of applying Starling-type forces to the *endothelial* lining to interpret fluid balance and homeostasis in most tissues has led to a similar approach being applied to pulmonary *epithelium*. In the lung, the endothelium is still regarded as the "primary line of defence" as Staub [84] terms it. However, the intercellular junctions appear much tighter in epithelium than in endothelium [80]. This is reflected in setting up Starling-type equations for the epithelium under normal physiological conditions [85] in which the protein permeability of epithelium is taken as exceedingly low [19, 68]. In quantifying osmotic efficiency, it is customary to use the Stavermann reflection coefficient, ranging from 0 for no osmotic pressure to 1 for a perfectly semi-permeable membrane. Thus pulmonary epithelium separating interstitial cells from the continuous liquid layer assumed to line the alveolus is attributed a reflection coefficient of 1 for protein, implying a maximal osmotic pressure.

Alveolar flooding

When alveolar flooding occurs there are two characteristics. First, "burst-through" onto the alveolar surface is relatively sudden [84, 85], occurring for an increase in lung weight of about 35%—that is, at a fairly advanced state of interstitial oedema. Second, the composition of alveolar oedema is the same as that of lung lymph and, hence, interstitial fluid [61, 91]. This is described as "disturbing" by those who apply Starling-type forces to the epithelium, since it implies no osmotic pressure across this membrane. It also implies a Stavermann reflection coefficient of zero.

It is very difficult to envisage a sudden switch in the reflection coefficient from 1 to 0—that is, from one extreme to the other—if there is a continuous liquid lining under normal physiological conditions and it is simply thickened by the accumulation of alveolar oedema. A more plausible explanation [42, 44] would be that Starling forces cannot apply at a pulmonary epithelial surface which is dry on one side as a result of water repellency. When the interstitial pressure exceeds the critical fluid penetration pressure, there is the relatively sudden burst-through characteristic of the onset of alveolar oedema, fluid exuding onto the alveolar surface essentially unchanged in composition.

Negative interstitial pressure

If there is no osmotic pressure generated across the epithelial membrane, one must either postulate dry areas on the alveolar surface to avoid the "bubble" or follow the conventional argument that interstitial pressure must be negative. Thus it is argued that it will balance the negative pressure arising in the continuous fluid lining by virtue of its concave curvature with respect to air. However, the surface tension must, once again, be near-zero, or interstitial pressure would need to be appreciably more negative than a limiting value of about −7 mm Hg considered physiologically feasible [32].

Much attention has therefore been focused on the argument for near-zero surface tension as discussed above and experimental evidence for a negative interstitial pressure. Experiments using wicks or other techniques in the lungs are open to alternative interpretations because of uncertainties in the microcurvature of the air–liquid interface. However, these objections do not apply to Guyton's epochal "ping-pong ball" experiment [31] in which negative pressures of approximately −7 mm Hg were recorded in subcutaneous sites in dogs. This writer has repeated those experiments but, when obtaining the same results, found an air bubble in the capsule [42]. Was this an artefact attributable to the inherent unsaturation of tissue with respect to gases [68]—that is, the same driving force which enables a collapsed lung to re-expand in the intact thoracic cavity?

Another disturbing feature of negative interstitial pressure is that some lung structure must be capable of withstanding it mechanically at the local level, and the alveolar septum would seem much too flaccid.

Conventional assumption

There is the tacit assumption in conventional theory that, because the interfacial component of recoil of the inflated lung leads to further collapse with the expulsion of air, this must be caused by a concave liquid (bubble) lining. Hence it is presumed that the liquid in the lining must have a negative pressure. In reality, all that liquid filling is telling us is that it reduces the net mechanical tension in the alveolar wall, whether this is transmitted by the surface tension of a liquid or the epithelial membrane itself. If the liquid lining is discontinuous with the dry areas mostly concave and the wet areas convex with respect to air, as shown in figure 9A, it is now possible to have the same lung recoil but with a positive rather than a negative pressure in whatever fluid is present. If oedema forms this will enlarge the pools which, for the same perimeter, will now become more convex and, with a lower radius of curvature (r in equation (1)) will give a larger value of P. This is now a positive driving force pushing fluid back across the alveolar membrane into the interstitium. Quite unlike the bubble model, these "corner pumps" [35] are self regulating, as r increases and P decreases as the oedema is resolved until P is equal to the interstitial value which, now, has no need to be negative. An interesting feature of the corner pump is that a surface tension appreciably greater than zero would be an advantage, not a disadvantage, in resolving oedema.

Alveolar fluid: convex or concave?

The foregoing model may seem to resolve the apparent conflict between lung recoil and a positive interstitial pressure, but the concept has been attacked on the grounds that electronmicrographs produced by the opponents [25] do not show fluid "bulging" into the alveoli with a contact angle at the triple point where the pool meets the apparently fluid-free epithelium. Rather, they show a remarkably smooth concave contour followed by both the liquid and tissue surfaces as depicted in figure 10B. Their electron microscope scans do show a contact angle, but this is formed by the tissue folding under to initiate the pleats described earlier, rather than by fluid bulging outwards.

The question of convex *vs* concave zones of the alveolar surface is one for which, unfortunately, electronmicrographs can be produced to support both sides of the argument, ranging from those of Gil and Weibel [28] which would be expected to be more flat for normal tissue, to oedematous lungs in which highly convex droplets have been demonstrated on the alveolar surface [18, 58] as the convex pumps fill. Moreover, the "moonscapes" of all back-scatter electronmicrographs show both convex and concave zones, so the question remains unresolved and a fascinating subject for debate.

OTHER ROLES OF SURFACTANT

In addition to its primary roles in pulmonary mechanics and fluid balance, already discussed in detail, several other functions have been proposed for surfactant in the lung.

Rheological role

Lecithins are used widely industrially as very effective viscosity modifiers [81], although drugs used to stimulate surfactant secretion in the lung had only minor effects, with no significant changes in viscosity or thixotropy [4]. However, Lachmann [59] has concluded that disturbances of the bronchial surfactant system can lead to mucostasis, impaired bronchial clearance, infection, ventilation–perfusion mismatching and hypoxia. The interest in mucus plugs has led Enhorning to propose a role for surfactant in asthma [21].

Lubrication

The lubrication of pleural sliding is traditionally attributed to a layer of pleural fluid [3], but such hydrodynamic lubrication is normally found only for fast-moving surfaces and, in any case, there is little doubt of direct pleural contact. Surfactant has been identified in pleural fluid and has been shown to be an excellent boundary lubricant [48] and to be directly adsorbed to the mesothelium, which it renders hydrophobic.

"Anti-glue" function

Anti-glue mechanisms have been proposed at the alveolar level by Reifenrath [74] and by Sanderson and colleagues [78] in analysing the unpleating of epithelial membrane in the pits and pools discussed earlier. In both studies, the surfactant was assumed to act at the liquid–air interface. Studies in our laboratory [38] have shown that surfactant is a particularly effective release agent when directly adsorbed onto *solid* surfaces such as the alveolar surface shown in figure 10. Lecithin is sold widely in spray cans as a most effective release agent for use on baking pans. It has also been proposed that surfactant in lung lymph can facilitate flow by maintaining patency of the lymphatic system [49].

Carcinostatic role

DPPC is such an effective release agent that it will even reduce by 90–99 % the force of adhesion of such potent glues as fibronectin [41]—the very tacky adhesive coating many highly malignant metastatic cells. It has been demonstrated how surfactant can migrate [47] to coat emboli "squeezing through" the pulmonary vasculature. If this also applies to metastatic cells it could explain the phenomenon known as the "first-organ encounter" which is known [83] to reduce metastatic potency. The lung is in a unique position to monitor organ-to-organ traffic of metastatic cells and so any effect of migrated surfactant in reducing the adhesive potency of fibronectin could confer a major carcinostatic role [39, 42].

Thus surfactant may possess many important functions in addition to those associated with the mechanics of the alveolus and its fluid balance while, in all of these roles, the possibility should always be considered that it can act directly at tissue surfaces in addition to the liquid–air interfaces of conventional theory.

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FACTORS INFLUENCING INTRAPULMONARY AIRWAY CALIBRE DURING ANAESTHESIA

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Intrapulmonary airway calibre is influenced by several factors, most important of which are: intrinsic tone of the smooth muscle, the presence or absence of oedema of the airway wall, and secretions in the airway lumen. This review will focus on mechanisms controlling airway tone in the absence and presence of drugs commonly used in anaesthesia, and on methods of measuring airway calibre during anaesthesia.

FACTORS MODULATING AIRWAY TONE

Intracellular Events

Smooth muscle contraction is largely responsible for the rapid changes in airway calibre seen during anaesthesia: a series of intracellular events in the smooth muscle lead to either contraction or relaxation. These intracellular processes are regulated by extracellular factors such as neurotransmitters, catecholamines or hormones which do not penetrate the cell membrane. They bind to specific receptors on cell surfaces which initiate a cascade of events that convert these signals (first messengers) into internal signals (second messengers) which induce biochemical changes in the smooth muscle cell, leading to contraction or relaxation (fig. 1).

In smooth muscle the conversion of external signals to changes in concentrations of intracellular second messengers involves a group of compounds called G-proteins which link the surface receptors to their effectors [32]. This receptor–G-protein interaction causes the release of guanosine diphosphate (GDP) from the guanine nucleotide binding site on the G-protein, allowing guanosine triphosphate (GTP) to bind. The GTP-bound form of the G-protein (the activated form) dissociates from the receptor and activates the effector protein, which then modulates intracellular concentrations of specific second messengers [103]. For example, in all cells, including airway smooth muscle cells, the G-protein G_s regulates the concentration of cyclic adenosine monophosphate (cAMP) in cells by activating the effector, adenylate cyclase, when a β-adrenergic agonist, such as adrenaline, binds to a β-adrenergic receptor [107]. More than one G-protein signalling system may mediate a given physiological effect and a single G-protein may modulate more than one effector [124].

Goldberg and colleagues [39] originally hypothesized that cyclic nucleotides might act as second messengers. Goldberg proposed that cAMP and cyclic guanosine monophosphate (cGMP) mediated antagonistic actions within cells such that increases in intracellular concentrations of cAMP were associated with smooth muscle relaxation, while increased concentrations of cGMP were associated with contraction. Although there is still much that we do not know about the signal transduction process, evidence to date suggests that increased concentrations of cGMP and of cAMP are associated with relaxation of smooth muscle. The role of cGMP as a second messenger involved in smooth muscle relaxation has been re-evaluated by Nakatsu and Diamond [90]. Nitrovasodilators, such as sodium nitroprusside, are now known to relax vascular smooth muscle by increasing intracellular concentrations of cGMP. Although evidence linking increases in cGMP to relaxation is strongest in vascular smooth muscle, similar mechanisms exist in airway smooth muscle [42].

KEY WORDS
Airway. intrapulmonary. Anaesthesia general.

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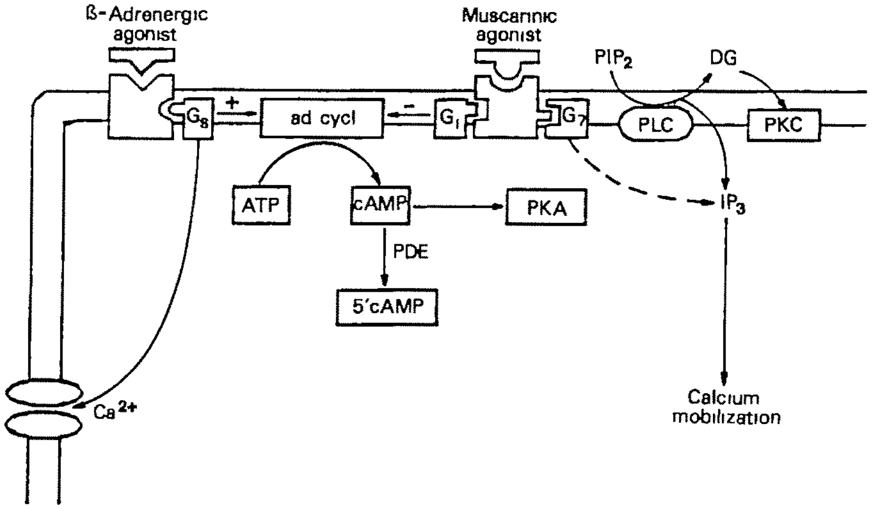

FIG. 1. Receptor–transducer–second messenger complex in airway smooth muscle. G_s = Stimulatory guanine nucleotide binding protein; G_i = inhibitory guanine nucleotide binding protein; $G_?$ = unknown nucleotide binding protein; ad. cycl. = adenylate cyclase; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; PDE = phosphodiesterase; PKA = protein kinase A; PLC = phospholipase C; PKC = protein kinase C; IP_3 = inositol 1,4,5-trisphosphate; PIP_2 = phosphatidylinositol 4,5-bisphosphate; DG = diacylglycerol.

Muscle contraction, in contrast to relaxation, involves increased cytosolic concentrations of calcium [96]. This results in phosphorylation of contractile proteins in the muscle, initiating cross bridging, which initiates or maintains smooth muscle tone. There are two basic mechanisms by which smooth muscle cells can increase this cytosolic calcium: via release of Ca^{2+} from intracellular stores which is mediated through surface receptors, and by entry of extracellular Ca^{2+} through voltage-dependent or receptor-operated voltage-independent calcium channels [29, 41]. Voltage-dependent calcium channels are blocked by calcium entry blockers such as nifedipine and verapamil.

Acetylcholine, α-adrenergic agonists and histamine often operate through a series of cell surface receptors and G-proteins linked to the phosphoinositide (PI) cycle [76, 103, 124]. A phospholipid component of the cell membrane is broken down into two second messengers. The end result is the liberation of calcium stored in the endoplasmic reticulum. This is a key event resulting ultimately in muscle contraction. At the same time, these receptors, via G-proteins, open receptor-operated calcium channels, allowing extracellular calcium to enter the smooth muscle, thereby increasing the cytosolic concentration of calcium and activating contraction [41]. A third way in which such agonists can increase airway tone is by inhibiting adenylate cyclase via the G-protein, G_i [60, 75, 112].

Extracellular Events Regulating Smooth Muscle Tone

Neural and humoral factors

Parasympathetic nervous system. Intrinsic airway tone is modulated by a complex combination of neural and humoral factors (fig. 2). The neural component is a series of reflex arcs. Afferent nerve terminals collect and transmit impulses via the vagus nerve for central processing. These afferents include slowly adapting receptors (stretch fibres) localized at smooth muscle of the conducting airways which are tonically active, rapidly adapting receptors (irritant), and unmyelinated C-fibres [126].

Parasympathetic nervous system stimulation plays a major role in the regulation of airway tone and secretions. Cholinergic efferent nerves arise in the vagal nuclei of the brainstem and pass down the vagus nerve to synapse at ganglia in airway walls. Relatively short postganglionic fibres pass to target cells. Postganglionic parasympathetic nerves release acetylcholine which activates muscarinic receptors on airway smooth muscle. This initiates the chain of events that mobilizes calcium and ends in muscle contraction [5, 70]. Thus vagal

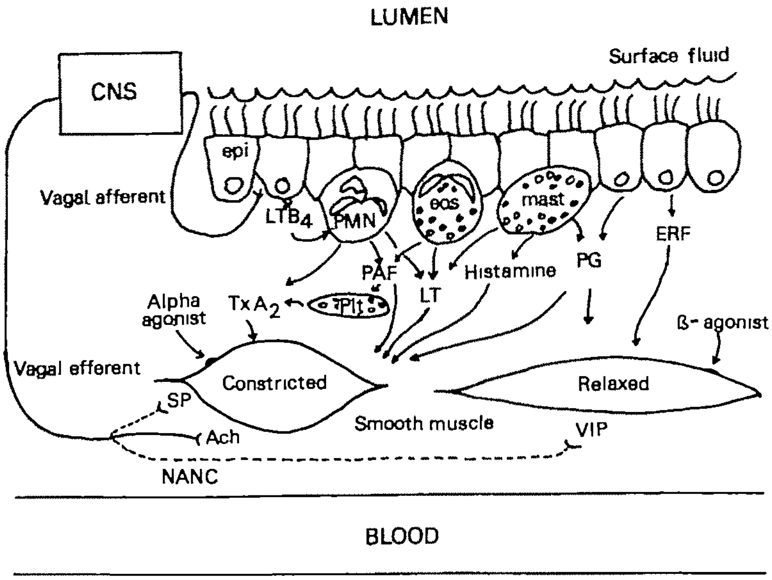

FIG. 2. Diagram of the component structures of the airway. CNS = Central nervous system; epi = epithelial cell; PMN = polymorphonuclear leucocyte; eos = eosinophil; mast = mast cell; LTB_4 = leukotriene B_4; LT = other leukotrienes; PAF = platelet activating factor; TxA_2 = thromboxane A_2; PG = prostaglandins; ERF = epithelium-derived relaxing factor; SP = substance P; Ach = acetylcholine; VIP = vasoactive intestinal polypeptide; NANC = non-cholinergic non-adrenergic efferent. (Modified from [31], with permission.)

nerve stimulation causes bronchoconstriction, which is potentiated by cholinesterase inhibitors and is blocked by muscarinic receptor antagonists.

Multiple muscarinic receptor subtypes have recently been identified. Atropine is a non-selective muscarinic blocking drug acting at all muscarinic receptor sites, whereas pirenzepine selectively blocks M_1 receptors and gallamine blocks M_2 receptors [6]. Studies using these blockers currently suggest that the M_1 receptor subtype modulates excitatory neurotransmission through lung parasympathetic airway ganglia. Thus pirenzepine, presumably by blocking M_1 receptors at the ganglia, inhibits the increase in pulmonary resistance provoked by vagal nerve stimulation in dogs [8] and rabbits [12] and inhibits vagally-mediated bronchoconstriction induced by sulphur dioxide in humans [69]. M_2 receptors in the airway are located presynaptically on postganglionic parasympathetic nerves [6] and inhibit release of acetylcholine [33]. M_2 receptor block with gallamine removes this inhibition and potentiates, rather than inhibits, bronchoconstriction. The muscarinic receptor located on the airway smooth muscle itself is thought to be of the M_3 subtype [6]. Muscarinic receptor antagonists have been in use for decades to treat irritant-induced vagally-mediated bronchoconstriction. Since atropine, glycopyrrolate and ipratropium are non-selective, they produce undesirable side effects on the central nervous system, heart and the gut [40]. The development of more selective muscarinic antagonists is underway and may prove clinically useful in the future.

Sympathetic nervous system and circulating catecholamines. Adrenergic nerve fibres are found largely in association with submucosal glands and bronchial arteries, but not in the smooth muscle of intrapulmonary airways [98]. Sympathetic nerves appear to modulate cholinergic neurotransmission at the ganglia. Although sympathetic innervation to the human lung is sparse, this system has marked influence on the regulation of airway tone via circulating adrenaline from adrenal secretion [98]. Adrenaline binds to β_2 receptors on airway smooth muscle and via the G-protein, G_s; and its effector, adenylate cyclase, increases cAMP (second messenger) and relaxes smooth muscle [32, 103]. β-Adrenergic agonists have several other beneficial actions on airways. They inhibit release of inflammatory mediators from mast cells [3] and increase clearance of airway mucus [89]. The few α-adrenoceptors in lung [7] are localized mostly to serous cells. Circulating noradrenaline has little influence on airway tone [125] and reactivity [110].

Non-adrenergic non-cholinergic nerves. Neural and humoral control of the airway is even more complex than previously thought and involves additional neural pathways that are neither cholinergic nor adrenergic. It is likely that a number of neuropeptides act as neurotransmitters for this system [79]. Both excitatory (constrictor) and inhibitory (dilator) mechanisms have been described [4, 61].

The neuropeptide of non-adrenergic non-cholinergic bronchodilator nerves may be vasoactive intestinal peptide (VIP), a 28-amino acid peptide that relaxes airway smooth muscle *in vitro* [101]. The density of VIP-immunoreactive nerves diminishes in the small airways, and specific binding sites are found in the airway smooth muscle layer [80]. The biological effects of VIP are mediated by its binding to specific cell surface receptors resulting in increases in cAMP production, but the precise pathway has not yet been elucidated. The importance of this mechanism in regulating airway tone is not known, as specific blockers are not yet available.

The excitatory neuropeptides include substance P and a group of other structurally related tachykinins. In addition to constricting airway smooth muscle [25, 113], these neuropeptides stimulate secretions, increase vascular permeability and release histamine from some types of mast cell [79]. Tachykinins are degraded by neutral endopeptidase (NEP) enzymes localized largely in the airway epithelium [13, 56]. Therefore, damage to the airway epithelium potentiates markedly the constrictor effects of these substances.

Epithelium

The epithelium can modulate airway calibre by virtue of its barrier function [58], by the production of constricting and relaxing factors [34] and by limiting peptide degradation [13, 56].

The airway is lined by a layer of epithelial cells which acts as a diffusion barrier to antigens, irritants and inhaled pharmacological agonists. In order to alter airway calibre, these agents must gain access to nerve fibres, mast cells and smooth muscle located beneath the epithelium (fig. 2).

Just as endothelial cells are important modulators of vascular tone, recent studies suggest that the epithelium of the airway is a metabolically active tissue that can modulate smooth muscle function by the production and destruction of inflammatory mediators such as prostaglandins, and perhaps non-prostanoid relaxing and constricting factors [34, 88].

Immunohistochemical and biochemical studies in human lung tissue demonstrate that neutral endopeptidases (enzymes that degrade neuropeptides such as substance P) are concentrated in epithelial cells [59]. Both NEP inhibition and epithelial removal [20] potentiate substance P-induced airway constriction. Thus a third way in which the epithelium might influence airway tone is by regulating the destruction of neuropeptides within the airway.

Therefore, damage to the epithelium increases access of luminal substances to muscle and to afferent nerve fibres that elicit the irritant bronchoconstrictor responses seen so often with airway instrumentation during anaesthesia. In addition to the loss of a diffusion barrier, epithelial damage may result in loss of an epithelium-derived relaxant factor and loss of enzymes which degrade constrictor neuropeptides. All three mechanisms could increase airway tone and reactivity.

Bronchial biopsies from patients with even mild asthma reveal extensive destruction of the ciliated epithelial cells [68]. Acute infections with many respiratory viruses are also associated with epithelial desquamation in humans [119]. In animal models infected with parainfluenza virus, both decreased concentrations of NEP and increased airway reactivity to substance P were documented [13, 56, 83]. Many years ago, Empy and coworkers [27] showed that the airway hyperreactivity produced by viral illness of the airway lasted for 3–6 weeks after symptomatic recovery. These more recent findings make Empy's observations somewhat easier to understand.

Inflammation

The presence of airway inflammation can alter airway tone and reactivity in a variety of different ways. The inflammatory response (tissue oedema and cellular infiltrates) can itself alter the structure of the airway so that a challenging agent results in an exaggerated response. Second, the products of the inflammatory response (histamine, leukotrienes, platelet activating factor, prostaglandins) themselves stimulate nerves and muscle of the airway by mechanisms described previously. Third, secretions produced by the inflammatory response further reduce the size of the airway lumen [87] (fig. 2).

Moreno and colleagues [86] demonstrate through simple geometric arguments that the ratio of airway wall area to airway cross-sectional area profoundly influences the change in airway resistance for the same degree of muscle shortening. If this ratio is increased by mucosal oedema or cellular infiltration, such a change could produce a trivial alteration in baseline airway calibre, but could profoundly alter the maximal constrictor response of the airway. We are often requested to anaesthetize patients who have inflammatory changes in their airways as a result of asthma, chronic bronchitis, viral infections and, less often, airway burns or smoke inhalation. Before the induction of anaesthesia, these inflamed airways are in a relaxed condition and the small increase in wall thickness results in only a small decrease in the diameter of the airway, so that the patient appears to be asymptomatic. However, placing a tracheal tube into this inflamed airway with increased wall thickness initiates an irritant reflex which now leads to marked increases in airway tone and perhaps complete closure of the airway [57]. The best way of managing patients who must come to anaesthesia with pre-existing inflammation is to treat the inflammation before operation, which means the administration of a short course of corticosteroids.

MEASUREMENT OF AIRWAY CALIBRE DURING ANAESTHESIA

General Principles

As we inspire and exhale, forces arise within the respiratory system which oppose its motion and seek to restore the system to its original resting dimensions and configuration. Practically, there are two such opposing and restoring forces: elastic resistance and flow (viscous or non-elastic) resistance. Elastic resistance is proportional to the volume of the respiratory system and is usually quantified as compliance:

$$\text{Compliance} = \frac{\text{Incremental change in volume (litre or ml)}}{\text{Incremental change in pressure (cm } H_2O \text{ or kPa)}}$$

$$\text{Resistance} = \frac{\text{Pressure across component of interest (cm } H_2O \text{ or kPa)}}{\text{Flow through the component (litre } s^{-1})}$$

Force applied to the respiratory system to overcome elastic resistance during inspiration is stored in this elastic component of the lung and chest wall and provides energy for exhalation. Non-elastic or flow resistance is proportional to gas flow rate and is quantified as resistance. It is unfortunate that the term "resistance", when unqualified, implies only flow or non-elastic resistance. Alternatively, the term "conductance" is used to quantify flow resistance. This is the reciprocal of resistance and is thus the flow produced by a unit of pressure applied across a structure (0.13 kPa litre^{-1} s). Force applied to the respiratory system to overcome flow resistance is dissipated and is not available to do subsequent work.

Clinical Applications

Airway calibre is evaluated by measuring the flow resistance of the airways. Forces opposing motion may originate in the airway as a consequence of friction between gas molecules themselves or between the gas molecules and the airway walls. As in other situations involving flow through tubes, a decrease in the calibre of the tubes is associated with increased resistance. As flow patterns along the branched air passages are highly complex, it is generally not possible to predict respiratory pressure–flow relationships from simple formulae such as Poiseuille's law. Resistance during respiration also originates in other components of the respiratory system because of friction between adjacent tissues of the lung and of the chest wall. The components of respiratory resistance and representative values are shown in figure 3.

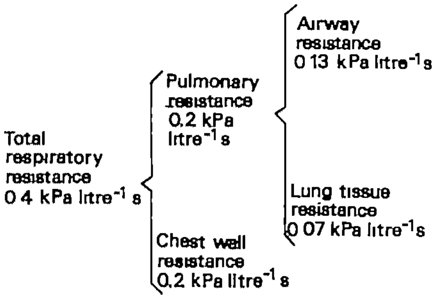
Total respiratory resistance 0 4 kPa litre^{-1} s
Pulmonary resistance 0.2 kPa litre^{-1} s
Airway resistance 0 13 kPa litre^{-1} s
Lung tissue resistance 0 07 kPa litre^{-1} s
Chest wall resistance 0.2 kPa litre^{-1} s

FIG. 3. Partition and subdivision of respiratory resistance, with representative values. Each component can be measured individually by simultaneous determination of flow and pressure across the element of interest. Resistances of both airways and lung tissue are components of pulmonary resistance. Both pulmonary resistance and chest wall resistance constitute total respiratory resistance.

In addition to airway tone, lung volume is an important determinant of flow resistance. Intrapulmonary airways are passively distended at large lung volumes by their connections with lung parenchyma and resistance is thus reciprocally related to lung volume. Therefore, a specified increase in airway tone produces a greater increase in resistance at a small lung volume than at a large lung volume [71].

Another change produced by alterations in airway calibre, when such changes are non-uniformly distributed throughout the lung, is the appearance of frequency-dependence of compliance. Normally, lung compliance remains fairly constant, because the respiratory frequency at which it is measured varies over a wide range. Since non-uniform bronchoconstriction occurs throughout the lung, pulmonary compliance appears to diminish as respiratory frequency increases.

There are many different methods for measuring resistance of the respiratory system and its components. Many are applicable in anaesthetized patients [10]. Measurement of actual airway resistance cannot be performed during anaesthesia because the necessary respiratory manoeuvres require conscious co-operation of the subject.

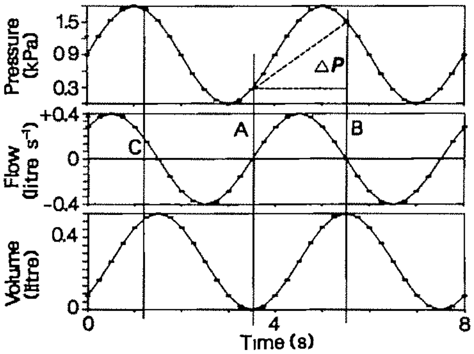

FIG. 4. Calculation of resistance from recordings of pressure, flow and volume during respiration using the method of Von Neergard and Wirz [118]. For determination of pulmonary resistance transpulmonary (alveolar–intrapleural [oesophageal]) pressure is measured. Instants of zero flow are identified (lines A and B). The entire pressure difference (ΔP) occurring between these instants is attributable to elastic forces. Lung compliance (C_L) can be estimated as difference in volume between times A and B divided by ΔP. To estimate pulmonary resistance at any time (e.g. line C), total pressure at that instant is noted. This total pressure consists of both elastic and flow resistive pressures. The elastic component is determined by dividing lung volume at that instant by C_L. This elastic pressure is subtracted from total pressure to give flow resistive pressure. Resistance is this flow resistive pressure divided by flow at that instant.

Therefore, in anaesthetized subjects, pulmonary or total respiratory resistance has been used to evaluate airway calibre and bronchomotor tone. This requires the reasonable assumption that, in many circumstances, the predominant fraction of change in total or pulmonary resistance is caused by change in the airway resistance component, while alterations in lung tissue and chest wall resistance remain minimal. It is also assumed that lung volume does not change significantly.

The most frequently used technique of assessment of pulmonary resistance in anaesthetized subjects utilizes a balloon placed in the oesophagus to estimate pleural pressure and a pneumotachograph to measure gas flow. The pneumotachograph signal is integrated electrically to obtain gas volumes. The signals may then be analysed either manually or by computer [118] (fig. 4). There is some question about the reliability of this method in supine subjects in whom motion of mediastinal structures over the balloon during respiration might produce spurious variations in pressure [47]. Under some circumstances an appreciable fraction of an alteration in pulmonary resistance might be attributable to a change in the lung tissue resistance component in addition to that in bronchomotor tone [115, 121].

Another technique particularly applicable to anaesthetized subjects measures specific lower airways conductance [62], which is the relationship between lung volume and respiratory resistance [71]. Using this method, the effects on airways of halothane, enflurane and isoflurane have been demonstrated [44, 72].

EFFECT OF DRUGS USED IN ANAESTHESIA ON AIRWAY CALIBRE

Inhalation Anaesthetics

The mechanisms by which potent inhalation anaesthetics affect airway calibre include blocking of airway reflexes, directly relaxing airway smooth muscle, inhibiting release of broncho-active inflammatory mediators and augmenting β-adrenergic tone.

The action of inhalation anaesthetics on airway reflexes has been studied for many years and the ability of halothane [46, 67], cyclopropane [46], ether [77] and enflurane [92] to block a wide variety of airway reflexes has been well established. From studies of Vettermann and colleagues [114] and Alexander and colleagues [2] halothane, enflurane and isoflurane are equieffective at inhibiting increases in pulmonary resistance provoked by vagal nerve stimulation when administered at equivalent MAC multiples. These agents appear to have similar mechanisms of action despite their different chemical structures.

The site in the reflex pathway blocked by inhalation anaesthetics is being investigated. In elegant studies using a nerve–muscle preparation Korenaga and colleagues [67] found that clinically relevant concentrations of halothane reduced the amount of acetylcholine released from nerve terminals in response to nerve stimulation and reduced the size of the muscle contraction. This suggests that inhalation anaesthetics such as halothane suppress the final step of the reflex pathway.

The relative importance of other mechanisms involved in the beneficial effects exerted by inhalation anaesthetics on airways is less clear. Using Basenji-greyhound dogs, we demonstrated that 1.5 MAC halothane and 1.5 MAC isoflurane only slightly attenuated methacholine-induced airway constriction and concluded, in agreement with another study in Basenji-greyhounds [102], that inhalation anaesthetics had only a small direct effect on airways [51]. We determined if halothane, in concentrations used clinically, had direct relaxant effects on airway smooth muscle by comparing histamine dose–response curves in the control state and during halothane anaesthesia. Histamine triggers airway constriction both by a direct effect on airway smooth muscle and by stimulation of irritant receptors. This latter component is blocked by atropine. Our study showed that histamine produced dose-related airway constriction, which was attenuated by atropine and by halothane to a similar extent. The use of atropine in combination with halothane anaesthesia failed to increase the protection, leading us to conclude that the major action of halothane in attenuating this airway constriction was primarily the result of inhibited vagal reflexes.

Using human skin mast cell preparations, Kettelkamp and colleagues [65] showed that halothane, in concentrations used in clinical anaesthesia, significantly reduced tubocurarine-induced histamine release. In an effort to understand the importance of this mechanism *in vivo*, Hermens and colleagues [45], using the plasma histamine concentration as a marker of mediator release, found that although halothane significantly attenuated the increase in pulmonary resistance produced by an antigen aerosol challenge, histamine concentrations were unchanged. They concluded that the major protective effect of halothane on airways was attributable to mechanisms other than inhibition of histamine release from mast cells.

The contention that halothane augments β-adrenergic tone has never been substantiated [66]. Indeed, if this were an important mechanism, the administration of β_2-adrenergic agonists would not protect against bronchospasm during inhalation anaesthesia. However, Tobias has clearly shown that salbutamol protects significantly against histamine-induced bronchoconstriction during halothane anaesthesia [109].

There are conflicting views as to the mechanism by which halothane exerts direct effects on airway smooth muscle. Fletcher and colleagues [30] suggested that halothane had a direct relaxant effect, while Korenaga and colleagues [67] showed that the direct relaxant effect of halothane on airways did indeed occur, but that this effect required halothane concentrations far greater than can safely be used *in vivo* in humans.

Inhalation anaesthetics in common use may alter resting airway calibre or may prevent or reverse increases in airway tone. Although virtually all studies show that potent inhalation anaesthetics are highly effective at clinically used concentrations in preventing or reversing airway constriction, there remains some doubt as to their effects on baseline airway tone. Halothane and enflurane decrease baseline airway tone in humans [72]. The effects of isoflurane on baseline airway tone have been controversial since 1974, when Rehder and co-workers [97] reported that respiratory resistance was increased in five human volunteers following induction of anaesthesia with isoflurane. However, Heneghan and colleagues [44] in man, Hirshman and colleagues [51] in dogs and Watney, Jordan and Hall [122] in ponies found that isoflurane showed no constrictor effect on baseline airway tone. The discrepancy between Rehder's study and the other three studies may have resulted from decreases in lung volume with induction of anaesthesia or from reflex effects caused by the tracheal tube.

Gold, Schwam and Goldberg [38] found no differences in intra- and postoperative respiratory complications in 148 patients with chronic obstructive pulmonary diseases (COPD), anaesthetized with isoflurane and halothane, and concluded that patients with COPD receiving isoflurane were at the same risk for developing respiratory complications as those receiving halothane.

In conclusion, the mechanisms by which inhalation anaesthetics decrease airway calibre and prevent or reverse bronchospasm are complex, but largely involve inhibition of neural pathways. Although halothane has been considered the inhalation anaesthetic of choice for patients with asthma and COPD, both enflurane and isoflurane are acceptable alternatives.

Induction Agents

Thiobarbiturates

The effects of thiobarbiturates on airway tone are particularly interesting because thiobarbiturates are thought to constrict as well as relax the airway. Deep barbiturate anaesthesia suppresses airway reflexes, while light anaesthesia with ultra-short-acting i.v. barbiturates produces relatively little depression of these reflexes [11, 48, 54, 55, 106]. The site of this depression is not known, but involves the efferent pathway of the irritant reflex and is associated with decreased release of acetylcholine from nerve endings [55].

There is evidence to indicate that thiopentone constricts airways, although the relevance of this evidence to our patients remains to be determined. In 1943, Adriani and Rovenstine [1] observed that human, rat and dog bronchi constricted when exposed to thiopentone. In contrast, Fletcher and colleagues [30] and Edney and Downes [26] found that thiopentone had no effect on baseline tone in guineapig tracheal chains. Lenox, Mitzner and Hirshman [73] found that, at concentrations in the clinical range, thiopentone caused dose-related constriction, but at concentrations slightly greater than those used clinically, it caused bronchodilatation.

Thiobarbiturates trigger skin mast cells (but probably not lung mast cells) to release histamine [50], which could theoretically provoke airway constriction in predisposed individuals. Clark and colleagues [17] reviewed 100 cases of adverse reactions to thiopentone and Althesin in the United Kingdom. In eight, bronchospasm was associated with flushing and hypotension following thiopentone, suggesting a "histaminoid reaction". Oxybarbiturates lack this property [50].

Retrospective clinical studies performed many years ago show either an association between the use of thiopentone and bronchospasm [37] or no association at all [94, 104]. Treatment of airway disease and anaesthetic techniques have changed over the past 25 years. Prospective clinical trials are needed to determine whether or not thiopentone is associated with an increased incidence of complications in normal individuals and, more importantly, in patients with lung disease.

The primary stimulus that precipitates bronchospasm during anaesthesia is irritant-induced bronchospasm provoked by the tracheal tube. Large doses of barbiturates block this reflex. Because the doses of thiobarbiturate that we use normally may not reliably accomplish this goal, potent inhalation anaesthetics may be used instead, and the choice of induction agent becomes unimportant. If inhalation anaesthesia is not possible, a non-barbiturate induction agent or an oxybarbiturate, rather than a thiobarbiturate, appears to be a reasonable choice. If the patient must receive a thiobarbiturate, a large dose rather than a small dose should probably be used.

Ketamine

The bronchodilator effects of ketamine have been apparent since the early clinical studies [18, 51]. Mechanisms to account for this include inhibition of vagal pathways [84], direct relaxation of airway smooth muscle [16, 82, 117, 120] and increases in endogenous catecholamines which relax the airway via β_2-adrenoceptors on airway smooth muscle [81, 91].

Studies showing direct relaxing effects of ketamine on smooth muscle used concentrations of ketamine greater than we usually use clinically [82, 120]. Administration of the drug by aerosol could allow enough ketamine to reach the airway smooth muscle and at the same time decrease undesirable side effects. A recent study by Rock and colleagues [99], however, failed to prevent or reverse histamine-induced airway constriction in guineapigs with a very small dose of aerosolized ketamine. A study using greater concentrations of ketamine would be useful.

In the Basenji-greyhound model of persistent airway hyper-reactivity we showed that ketamine, in clinically used concentrations, prevented antigen-induced bronchospasm [49]. However, this protective effect of ketamine was abolished by β-adrenergic block, suggesting that the sympathomimetic effects are mainly responsible for its protective action on airways *in vivo*.

Ketamine appears useful in patients with reactive airway disease who require rapid induction of anaesthesia and tracheal intubation before deep inhalation anaesthesia can be achieved. It is also helpful in the treatment and in the emergency tracheal intubation of patients with status asthmaticus [74, 100, 108].

Neuromuscular Blocking Drugs

Neuromuscular blocking drugs possess two characteristics which can, at least theoretically, alter airway tone and reactivity: they are capable of inducing histamine release from mast cells lining the vessels into which they are injected [95] and, in order to interact with receptors at the neuromuscular junction, they must structurally resemble acetylcholine. Thus it is likely that these drugs will also bind to muscarinic receptors located on ganglia, nerve endings and airway smooth muscle and interact with cholinesterases, altering neurally mediated control of airway calibre [14].

Both tubocurarine [95] and atracurium [93] are potent releasers of histamine. However, the evidence showing a relationship between release of histamine and increased airway tone is less than compelling. In histamine infusion studies [53, 64, 78, 116] airway resistance, to our knowledge, was not measured. Nor was bronchospasm mentioned as a symptom, even at the greatest concentrations infused. Crago and colleagues [19], Simpson, Wright and Hammond [105] and Gerbershagan and Bergman [36] failed to find significant increases in airway tone after administration of tubocurarine to normal subjects. However, Crago and colleagues [19] did find greater airway resistance in subjects with pre-existing lung disease paralysed with tubocurarine, than with pancuronium, but did not follow up this observation with histamine receptor antagonist studies.

It is obviously preferable that neuromuscular blocking drugs do not block muscarinic receptors, since block of the M_2 muscarinic receptor subtype removes an influence inhibitory to acetylcholine release. Gallamine is an M_2-selective antagonist. Fryer and Maclagan [33] showed that gallamine potentiated vagally mediated airway constriction in guineapigs. Vettermann and colleagues [114], in an analogous study in dogs, showed that atracurium and low-dose pancuronium potentiated the increase in pulmonary resistance produced by vagal nerve stimulation, while vecuronium had no such effect. Perhaps atracurium and pancuronium share with gallamine the property of M_2 receptor antagonism.

By virtue of their chemical similarities to acetylcholine, all neuromuscular blocking drugs interact with cholinesterases. Until recently it has not been clear that they do this in concentrations used to produce muscle relaxation. Kaise and colleagues in our laboratory [63] showed that suxamethonium, in concentrations used clinically, potentiated acetylcholine- but not methacholine-induced airway constriction and that this effect was independent of ganglionic block, meaning that the effects were not neurally mediated.

Cholinesterase inhibitors such as neostigmine, physostigmine and edrophonium provoke airway constriction [85] by inhibiting the destruction of endogenously released acetylcholine at the parasympathetic efferent nerve terminals. These effects can be prevented and, it is hoped, reversed by muscarinic receptor antagonists.

Although there are many ways in which neuromuscular blocking drugs can theoretically increase airway tone and reactivity, there are few controlled studies addressing this subject in humans or animal models. Chemists are now able to synthesize neuromuscular blocking drugs which avoid most of the unwanted side effects. It seems reasonable to select neuromuscular blocking drugs which lack M_2 receptor blocking or histamine releasing properties for those patients at risk for developing bronchoconstriction during anaesthesia.

Local Anaesthetics

Local anaesthetic agents, administered either systemically or as aerosols, have been used to treat bronchospasm for many years. The mechanisms involved include direct effects on airway smooth muscle, inhibition of mediator release and interruption of reflex arcs.

In vitro studies demonstrated that local anaesthetics such as lignocaine can directly relax airway smooth muscle [24, 123] and inhibit release of mediators [123]. However, the drug concentrations required were about 100 times greater than the plasma concentrations that can safely be achieved *in vivo* in humans [22]. This suggests that, at clinical concentrations, local anaesthetic agents prevent irritant-induced bronchospasm primarily by blocking airway reflexes [15, 21]. Aerosol administration offers no advantage over the i.v. route [22] and may provoke bronchoconstriction. Procaine, hexylcaine and bupivacaine offer no advantage over lignocaine in this regard [23].

CONCLUSIONS

Airway calibre is determined by the intrinsic tone of the smooth muscle of the airway, in addition to airway wall oedema and luminal secretions. The rapid changes in airway calibre seen during anaesthesia after airway instrumentation result largely from parasympathetic nervous system activation of airway smooth muscle. Inhalation anaesthetic agents are extremely effective inhibitors of irritant-induced bronchoconstriction, as are local anaesthetics. The effects of thiobarbiturates on airway calibre are controversial, while the effects of neuromuscular blocking drugs are probably minimal. The benzodiazepines have no significant effects in asthmatic patients [43], while the effects of opioids are small and inconsistent [9, 28, 35, 111].

Studies using isolated airway tissue and animal models have identified many factors controlling airway calibre in the absence and presence of anaesthesia. These observations suggest many better ways of caring for our patients. However, only controlled clinical studies can truly determine which agents are appropriate for use in patients, especially those with pre-existing airway disease.

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RESPIRATORY MUSCLE FATIGUE: MECHANISMS, EVALUATION AND THERAPY

J. MOXHAM

Stimulated by the research of the Montreal Group in the mid and late 1970s, there has now been more than a decade of intensive study of respiratory muscle fatigue. Roussos and Macklem [61] demonstrated elegantly that the endurance of the diaphragm was similar to other skeletal muscles and that large inspiratory resistive loads could be sustained for only short periods, whereas loads of less than 40% of maximum could be sustained indefinitely. Other complementary studies followed, investigating endurance time and the fatigue of the respiratory muscles in a variety of physiological situations, including hypoxia and hyperinflation [28, 60]. What was the relevance of these findings to patients, particularly those with breathlessness and respiratory failure? The Montreal Group extrapolated from their research findings and postulated (and promulgated) that respiratory muscle fatigue was a key factor in hypercapnic respiratory failure [59]. The conclusion that fatigue is crucial to ventilatory failure has led to the suggestion that many hypercapnic patients have "chronic" respiratory muscle fatigue [58].

Before accepting the central role of respiratory muscle fatigue (acute or chronic) in ventilatory failure and determining its clinical significance, it is necessary to be able to define and then identify such "fatigue". A workable definition of muscle fatigue is the inability to sustain tension with repeated activity [16]. The question arises, of course, as to whether this failure to sustain force (or work) is the result of the subject not trying hard enough or perhaps a weak link in the chain of events from the central nervous system to the peripheral contractile apparatus (fig. 1).

Studies on skeletal muscle using animal models and also in man, both *in vivo* and *in vitro*, have focused on the key areas of the command chain depicted in figure 1 in an attempt to highlight the weak link and thus the primary site of fatigue. One possibility is that the central nervous system fails optimally to drive peripheral muscle (so called "central fatigue").

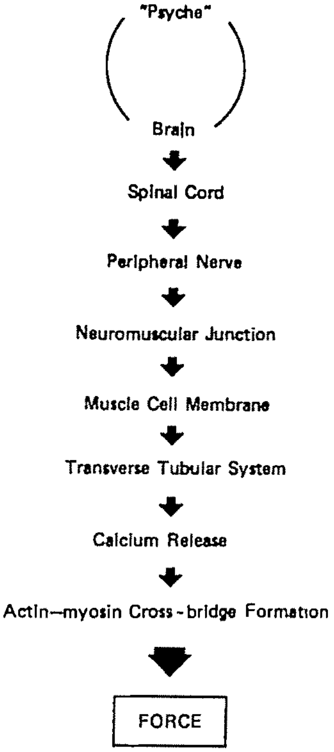

FIG. 1. Command chain for voluntary contraction of skeletal muscle. (Reproduced, with permission, from [16].)

Central fatigue

Central fatigue has long been documented for sustained, highload voluntary contractions of limb

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Muscle: respiratory, fatigue.

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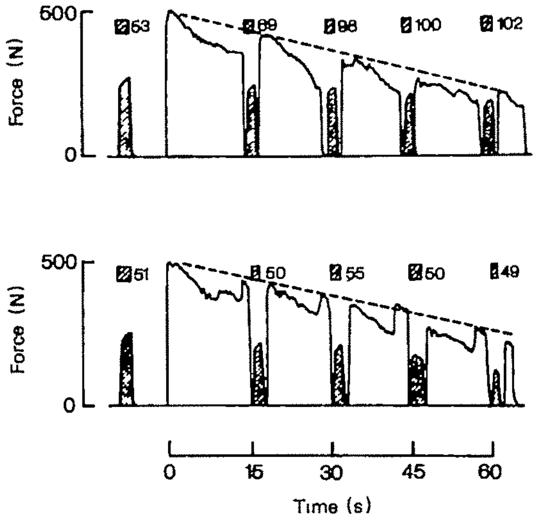

FIG. 2. Central fatigue (quadricep muscle). Top: Before a prolonged maximum voluntary contraction (MVC) is begun, percutaneous electrical stimulation (shaded) produces 53% of maximum force. As the MVC continues there is excessive force loss, stimulated force becoming a higher percentage of voluntary force, confirming inadequate activation (central fatigue). Bottom: In a repeat study, central fatigue is overcome when the subject is asked to make extra efforts before each stimulation period (stimulated force remains a steady percentage of voluntary force). (Reproduced, with permission, from [11].)

muscle [11, 12] (fig. 2). While seemingly performing of their best, subjects exhorted to do better *are* able to improve force generation. Submaximal central activation can be demonstrated elegantly by the technique of twitch interpolation [41]: during a low force voluntary contraction, a superimposed electrical stimulus produces a twitch response; during maximum voluntary contractions, all motor units can be fully activated and an added stimulus, therefore, causes no twitch response; the decline in the superimposed twitch is proportional to the level of voluntary activation and the level of central activation can, therefore, be determined from the twitch response. The technique has been used to study central fatigue of the diaphragm during prolonged inspiratory loading in normal subjects [9]. Bellemare and Bigland-Ritchie demonstrated substantial central fatigue of the diaphragm at the point at which subjects failed to meet target respiratory pressures. They concluded that central fatigue was responsible for approximately 50% of performance failure. They and others have extrapolated from these observations in highly motivated physiologists to conclude that central fatigue is likely to be important in clinical ventilatory failure. However, it is known that central fatigue is very dependent on the task involved, with prolonged, tedious and boring tasks producing more central fatigue than short term fatiguing loads [11, 41]. In the earlier studies in limb muscles, some subjects did not exhibit central fatigue and it therefore remains uncertain if such fatigue, varying from person to person and between tasks, is of any relevance to ventilatory failure. Studies in patients are clearly needed.

If central fatigue is unlikely to be the "weak link" in the command chain the next question is: can the more peripheral neuromuscular components respond to central drive without fatigue?

Peripheral fatigue

During maximum voluntary contractions central motor neurone firing frequency is initially very high (the force generated matches that following 100 Hz supramaximal electrical stimulation [41]). Studies in patients with respiratory failure indicate that they have very high central drive [22, 54]. The central drive in patients with chronic obstructive pulmonary disease and hypercapnia may be as high as 50% of maximum drive [22]. Given the curvilinear relationship between firing frequency and tension generation (frequency–force curve), any additional tension requirement (e.g. exercise or increased airways resistance) demands a disproportionately high central firing frequency (fig. 3). What, then, is the response of peripheral muscle to high frequency stimulation?

High frequency fatigue

High frequency nerve stimulation generates maximum tension from muscle, but rapid force loss occurs as stimulation continues (fig. 4). Lower frequency stimulation produces less initial force, as expected, but tension is well maintained and soon exceeds that of high frequency stimulation. The rapid force loss with high frequency stimulation is the result of failure of excitation (failure of propagation at the neuromuscular junction and muscle cell membrane), and therefore is paralleled by a progressive reduction in the EMG signal. Were such fatigue to develop in the respiratory muscles, rapid, "catastrophic" [18] force loss and respiratory pump failure would follow. Although one study of the effect of exhaustive, inspiratory loading in rabbits has demonstrated excitation failure [1], high frequency fatigue has not been

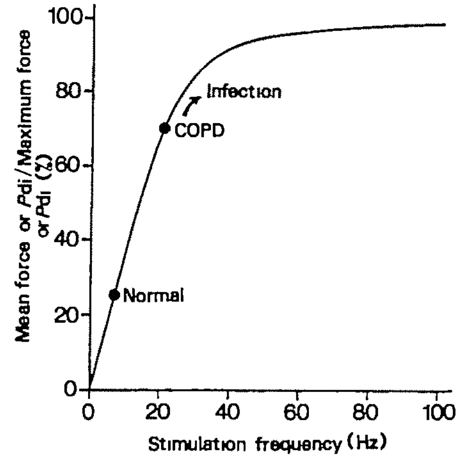

FIG. 3. Frequency–force curve of skeletal muscle (including the respiratory muscles). Patients with severe pulmonary disease (e.g. COPD) are likely to be placed at the top of the steep section of the curve. Any increase in muscle tension requirement demands a disproportionately large increase in motor neurone firing frequency. (Reproduced, with permission, from [36].)

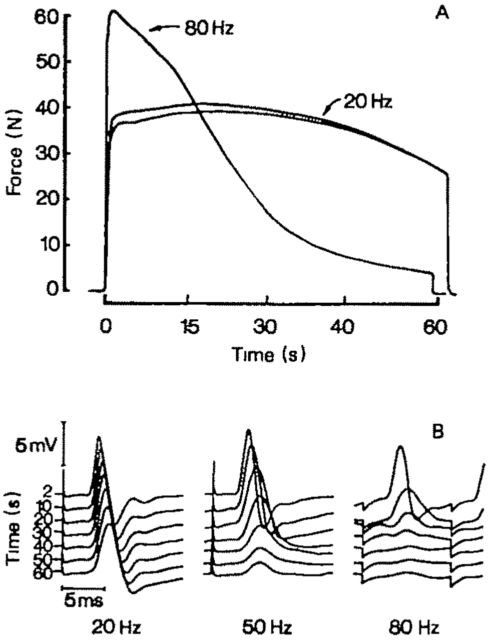

FIG. 4. A: Electrical stimulation of the ulnar nerve at a high frequency (80 Hz) results in rapid force loss in the adductor pollicis muscle, whereas stimulation at a lower frequency (20 Hz), produces a smaller initial force which is well maintained. B: The muscle action potential decreases rapidly at 80 Hz, but is unchanged at 20 Hz. (Reproduced, with permission, from [11].)

demonstrated following physiological exercise in man and it is doubtful whether such excitation failure ever contributes to force failure [42].

When seeking to maximize muscle tension, what strategies can be adopted if high frequency fatigue is to be avoided?

Central wisdom

When trained subjects sustain a prolonged voluntary contraction of a limb muscle there is gradual force loss (fig. 5) [11] and, over the second half of the contraction, a parallel gradual decrease in EMG activity. The force profile of the muscle can be mimicked by nerve stimulation. Initially, high frequency stimulation is required to match the maximum voluntary contraction (MVC), but the frequency must then be progressively reduced to optimize force generation. If stimulation frequency is increased during the study, force is not increased (i.e. there is no central fatigue); rather it decreases as a consequence of high frequency fatigue.

These studies suggest that during a prolonged, maximum, voluntary effort there is a gradual reduction in central firing frequency to optimize force generation (notwithstanding the gradual decrease in tension), and the CNS exerts a "central wisdom", thus avoiding the adverse effects on tension generation of both central fatigue and high frequency fatigue. Although it has not been demonstrated that the same central wisdom occurs in progressive hypercapnic ventilatory failure, there are no data to suggest otherwise. When considering techniques of detecting the weak links in the command chain, and if the analysis above is correct, it is almost certainly a fruitless task seeking to demonstrate central fatigue or high frequency fatigue in patients with ventilatory failure.

Low frequency fatigue

If the CNS modifies central drive to optimize muscle excitation, the question then arises as to whether distal, peripheral, contractile failure occurs. Is the weak link in the chain the peripheral contractile machinery? Electrical stimulation techniques may be used to investigate such possibilities and the contractile characteristics of many skeletal muscles, including the diaphragm and sternomastoid have been studied extensively [5, 16, 17, 20, 49, 50]. In man the diaphragm can be stimulated via the phenic nerve and contractile responses documented in terms of trans-

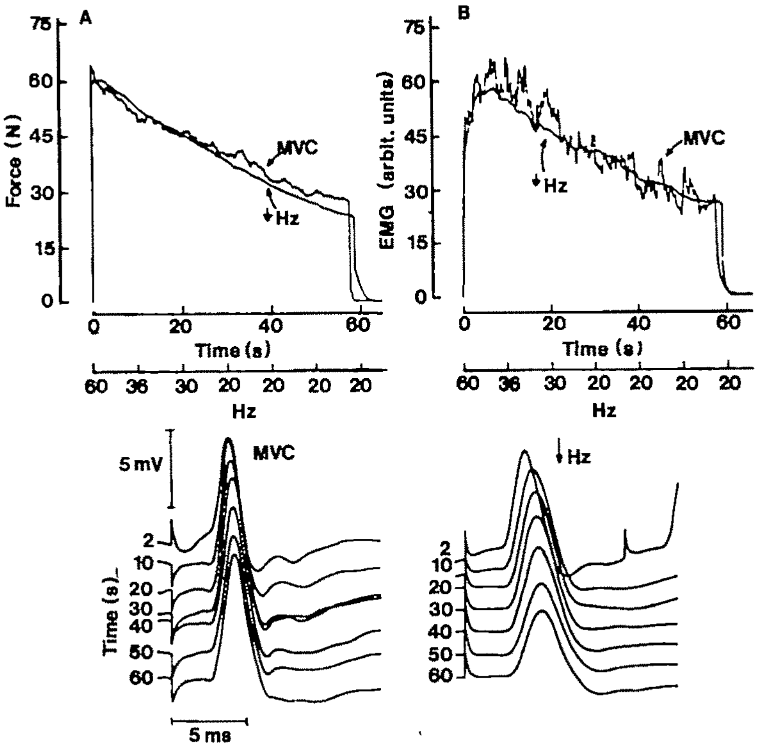

FIG. 5. Top: Maximum voluntary contractions (MVC) of the adductor pollicis muscle sustained for 60 s. A: During an electrically stimulated contraction, the force of the MVC is matched by initial stimulation at 60 Hz, followed by progressive reduction of the stimulation frequency to 20 Hz. B: The surface EMG for voluntary and stimulated contractions are closely matched. Bottom: The EMG M-waves during MVC and stimulated contractions are well maintained. (Reproduced, with permission, from [11].)

diaphragmatic pressure (*Pdi*) (fig. 6). Severe prolonged exhaustive inspiratory loading reduces the contractility of the diaphragm, and the frequency–force curve shifts to the right; the force reduction is particularly pronounced in response to low frequency stimulation (low frequency fatigue). When experimentally induced, this type of fatigue is long lasting [19] (minutes or hours) and associated with much damage of muscle fibres, demonstrable by electron myography [55].

Low frequency fatigue of the respiratory muscles would be expected to impair force generation at physiological firing frequencies, and has been shown to reduce the ventilatory response to carbon dioxide [52]. For some time, low frequency fatigue was considered to be a potentially important aspect of ventilatory failure [51]. However, the development of this type of fatigue requires massive loading—possible in the physiology laboratory, but of debatable relevance to clinical ventilatory failure. Furthermore, with the ex-

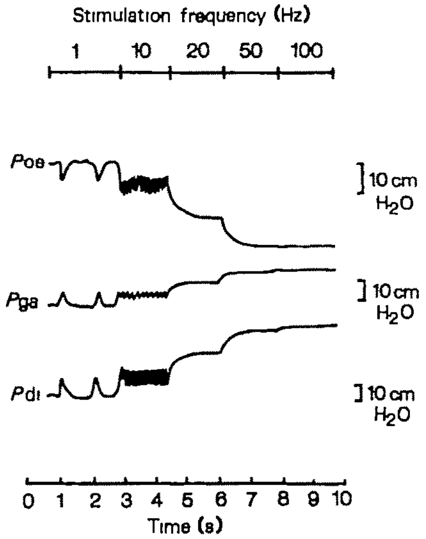

FIG. 6. Oesophageal (*Poe*), gastric (*Pga*) and transdiaphragmatic (*Pdi*) pressures with stimulation of the right phrenic nerve at 1, 10, 20, 50 and 100 Hz in a normal rested subject. (Reproduced, with permission, from [47].)

ception of a few case reports [51], it has proved very difficult to document low frequency fatigue of the respiratory muscles in the clinical setting. The difficulty of demonstrating low frequency fatigue may reflect the problems of applying sophisticated techniques to sick patients, but it may also be because overt low frequency fatigue, with consequent muscle damage, does not readily occur in the clinical context because the CNS will not (or cannot) drive the peripheral contractile apparatus sufficiently hard.

Thus it may be that, during progressive force failure, the respiratory muscle output is optimized by central nervous system control to avoid central fatigue, high frequency fatigue and low frequency fatigue. In the respiratory system, it may be that central drive is modified to avoid these types of overt fatigue and thereby optimize ventilation, albeit at the cost of hypercapnia. Support of the concept that central nervous system output is modified to avoid overt fatigue comes from studies of patients failing to wean from mechanical ventilation [65]. When the load on the respiratory muscles, necessary to achieve adequate ventilation, is so great as to be unsustainable (a very high tension time–index [10] see below), patients adopt rapid and shallow patterns of breathing (fig. 7). This reduces the work of breathing and can be sustained, but only at the cost of hypercapnia and acidosis, causing weaning failure.

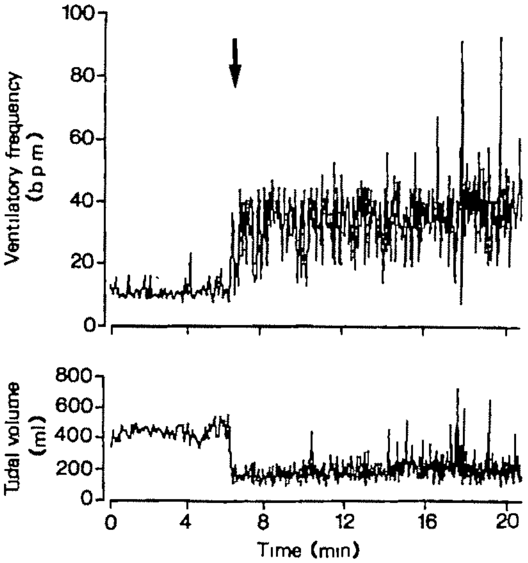

FIG. 7. Ventilatory frequency and tidal volume in a patient discontinued from ventilatory support (arrow) during a weaning trial. The patient developed hypercapnia and acidosis, and failed to wean. Note the rapid, shallow respiration immediately mechanical ventilation was withdrawn. (Reproduced, with permission, from [65].)

THE PROCESS OF FATIGUE

Fatigue is best understood, not as a single event, but as a continuous "process" that starts when a muscle is subjected to a sufficiently heavy load that will eventually become unsustainable. As time passes, a multitude of physiological alterations occur within the loaded muscle and along the whole length of the command chain. Although the tension generated decreases progressively, dangerous energy depletion (leading to rigor), muscle damage and excitation failure probably do not occur, because of the adaptive modification of central drive. To determine that a load is potentially fatiguing, one approach would be to use techniques that can detect the early physiological responses to excessive loading.

Early Changes in the Process of Fatigue

The electromyogram (EMG)

When skeletal muscle undertakes a high load contraction which sooner or later will not be sustainable, the EMG signal alters. There is a progressive reduction in the high frequency component of the signal, relative to lower frequencies. This reduction in the EMG "high : low" frequency ratio occurs early during fatiguing contractions and precedes force loss. These EMG changes are a signal that the muscle is heavily loaded and that the fatigue process is underway. As yet the cause of the EMG power spectrum shift is unknown [62].

Since EMG measurements are non-invasive, it had been hoped that this technique would be helpful in predicting respiratory muscle fatigue in patients. Some studies have indeed shown a decrease in the respiratory muscle high : low ratio during weaning failure [14]. However, because no absolute high : low ratio is associated with the fatiguing process, it is necessary to monitor the EMG for change, and this has proved difficult in the clinical situation. An additional problem is that alterations of lung volume and the pattern of breathing also influence the high : low ratio. The initial promise of this technique for detecting fatiguing loads has, therefore, not been fulfilled.

Maximum relaxation rate

The rate of decline of tension following contraction of skeletal muscle is an active, energy-

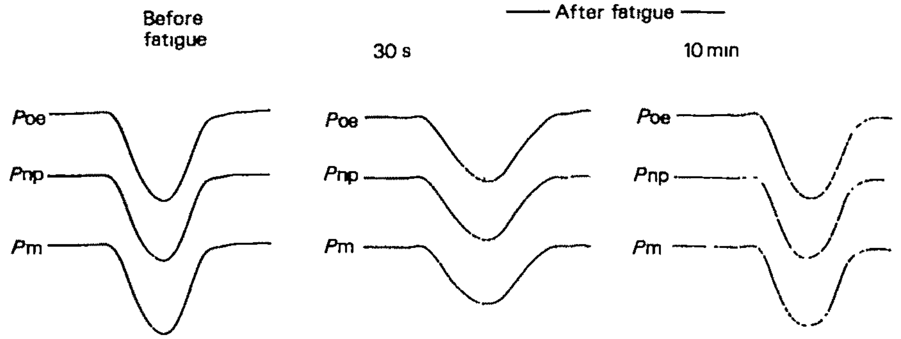

FIG. 8. Pressure measured in the oesophagus (*P*oe), nasopharynx (*P*np) and mouth (*P*m) during a sniff manoeuvre in a normal subject, before, 30 s after and 10 min after inspiratory resistive loading to exhaustion. Note the reduced slope of the pressure wave with fatigue (reflecting the slowing of muscle contraction and relaxation) and the subsequent recovery. (Reproduced, with permission, from [33].)

consuming process and not simply a passive event. The maximum relaxation rate (MRR) can be measured and expressed as the percentage force loss in 10 ms [66]. MRR is slowed by cold and hypothyroidism. It also slows early in the fatiguing process before force loss. MRR can be measured from voluntary or stimulated contractions and, for the respiratory muscles, from mouth, nasopharyngeal, oesophageal or transdiaphragmatic pressures. Several investigators have demonstrated slowing of MRR with exhaustive inspiratory loading in man [21, 37]. In normal subjects and patients with respiratory muscle weakness, pressures in the mouth and nasopharynx closely reflect those in the oesophagus during a natural sniff [32]. Inspiratory loading causes slowing of MRR in all sites, with mouth and nasal pressure measurements having the advantage of being less invasive [33] (fig. 8). The natural sniff is an excellent manoeuvre for generating wave forms suitable for MRR assessment and patients can be taught to sniff without difficulty. The sniff manoeuvre generates high pressures because the nose has a collapsible flow limiting segment (the nasal valve), which acts as a Starling resistor [32]. Thus during a sniff the nose narrows and large intrathoracic pressures are generated. Intubated patients are, of course, unable to sniff naturally, but they can perform sniff-like manoeuvres if a Starling resistor (acting as an artificial nose) is attached to the tracheal tube. Studies in normal subjects with such a device demonstrate that the pressure amplitude and MRR in the airway closely reflects oesophageal pressure and the slowing of MRR following inspiratory loading is detected easily [24]. Of the available early indicators of the fatiguing process, the measurements of MRR may be the most applicable to clinical situations.

Recent studies of MRR in sustained, maximum, voluntary ventilation (MVV) [53] have shown a progressive slowing of MRR during MVV, but no slowing with levels of ventilation that are a small fraction below maximum. This suggests that truly maximum ventilation is associated with the onset of the process of muscle fatigue, and that during MVV the respiratory muscles can be driven very hard (i.e. without significant central fatigue). Furthermore, slowing of MRR (for example, during weaning) indicates that the respiratory muscles are being subjected to an unsustainable load and ventilation will fail. Studies of MRR in weaning are currently being undertaken and in several patients failing to wean, relaxation has slowed, with prompt recovery when mechanical ventilation was reinstituted [J. Goldstone, personal communication].

Respiratory muscle load and capacity

The onset of the fatiguing process occurs when the load imposed on the respiratory muscles is excessive when related to pump capacity (fig. 9). Many studies have investigated fatiguing loads in normal subjects and have concluded that, when the mean inspiratory pressure is a high fraction of maximum pressure (a high tension time index (TTI)), fatigue will develop. Thus a load is fatiguing if:

$$P\text{m}/P\text{Imax} \times T\text{I}/T\text{T} = > 0.15\text{–}0.2$$

where Pm = mean inspiratory pressure; PImax = maximum inspiratory pressure; TI = inspiratory

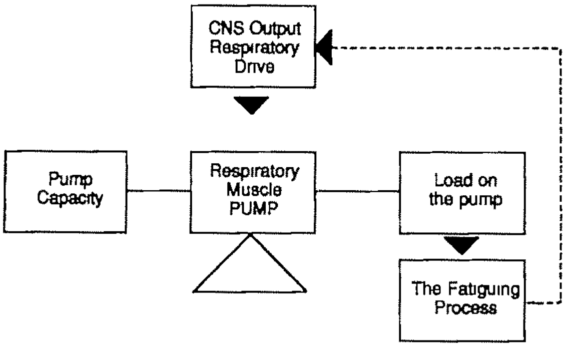

FIG. 9. Scheme to illustrate the central importance of the respiratory muscle pump and the crucial balance between load and capacity. When the ratio of load to capacity is high, fatigue could develop, but overt high frequency or low frequency fatigue are averted by adaptation of central drive. (Modified and reproduced, with permission, from [23].)

time; T_T = duration of a complete respiratory cycle [10].

Mean inspiratory muscle pressure is a function of tidal volume (V_T) and dynamic compliance ($C\text{dyn}$) in addition to inspiratory time. Milic-Emili has reconsidered the equation and elaborated the "Inspiratory Effort Quotient" (IEQ) [46]. Thus at FRC:

$$\frac{(K.V_T/C\text{dyn}) \times (T_I/T_T)}{P_I\text{max}} = \text{IEQ}$$

where K is a constant dependant on the shape of the inspiratory driving pressure wave, and is approximately 0.75.

These equations work quite well in the laboratory, but are more difficult to apply in clinical situations. A major problem is the measurement of $P_I$max in sick patients, and the value of $P_I$max is, of course, a major determinant of the IEQ or TTI. $P_I$max is conventionally measured by asking patients to make a maximum inspiratory effort from FRC or residual volume (RV) against an occluded airway; a manoeuvre that many patients with an intubated trachea find difficult. Greater patient effort can be achieved by occluding inspiration for periods of up to 20 s, during which patients make greater and greater inspiratory efforts, and $P_I$max is greater with this method [40]. A second problem is the theoretical one that static $P_I$max is probably not an appropriate measurement of the maximum capacity of the inspiratory muscles for dynamic manoeuvres. Since the respiratory muscles shorten during inspiration, the maximum available pressure for inspiration will be considerably less than the static $P_I$max. These considerations make an absolute "threshold" value for a fatiguing TTI or IEQ misleading. However, it is clear that success or failure in weaning is related to respiratory muscle load in relation to capacity and much research is currently being undertaken to assess the load on the respiratory muscles, and their capacity, in the Intensive Care Unit. The measurement of tidal volume, and pressure swings within the thorax, is teaching us much about the work of breathing in these patients, and the observation that unsustainable loads and, therefore, weaning failure is associated with rapid, shallow breathing is clinically important [64]. From the work of Tobin and colleagues, it has become clear that in the adult a rate of ventilation > 25 b.p.m. or a tidal volume of < 300 ml is commonly associated with weaning failure [65].

Measurement of $P_{0.1}$ has been used to assess respiratory muscle fatigue and predict weaning failure [38]. $P_{0.1}$ reflects the final pressure generation of the respiratory system and therefore reflects central drive, peripheral neuromuscular activation, generation of muscle tension and the translation of tension into inspiratory pressure. A high $P_{0.1}$ indicates high neuromuscular activation in response to a large respiratory load. Thus a high $P_{0.1}$ suggests that ventilation may eventually fail. However, of more importance is the relationship between load and maximum sustainable capacity (as embodied in the TTI or the IEQ). Therefore the measurement of $P_{0.1}$ provides only limited information.

THERAPEUTIC STRATEGIES

From a therapeutic point of view all three key determinants of respiratory muscle pump function (fig. 9) require careful consideration: is central drive optimal; is the respiratory load as low as possible; and has pump capacity been maximized?

Respiratory drive. Available data suggest that, in most circumstances, central drive is appropriate to drive the respiratory muscle pump optimally in order to meet its load most effectively. If inadequate drive were a problem, it would be expected that respiratory stimulants (e.g. doxapram, almitrine) would be helpful. Such drugs sometimes produce short term improvements in ventilation, but often at the cost of excessive

TABLE I. *Factors reducing respiratory muscle force and pressure generation*

Muscle shortening (length–tension relationship)
Diaphragm flattening (law of Laplace)
Increased inspiratory flow rate (force–velocity relationship)
Weakness (including neuromuscular block)
Fatigue

TABLE II. *Metabolic abnormalities that impair muscle contractility*

Hypophosphataemia
Hypomagnesaemia
Hypokalaemia
Hyper- and hypothyroidism
Steroid therapy
Other drugs (e.g. myasthenic syndromes)
Hypoxia
Hypercapnia

breathlessness. From a theoretical point of view, over-stimulation of the CNS with consequent over-riding of "central wisdom" is likely eventually to intensify fatigue and be counter-productive. In patients with CNS depression caused by drugs (e.g. diazepam, morphine), therapeutic stimulation of respiratory drive is, of course, one approach to the management of ventilatory failure.

Ventilatory load. Excessive ventilatory load is the most common cause of imbalance in the drive–load–capacity relationship. Increased airways resistance (chronic obstructive pulmonary disease (COPD), asthma) and reduced compliance (pulmonary oedema, fibrosis) are common problems. Factors increasing ventilatory requirements (exercise, fever, sepsis, hypoxia, carbohydrate loading, *etc.*), all impose an increased load. This load is reflected by the mean inspiratory pressure *Pm* in the TTI, and influences tidal volume, respiratory timing and dynamic compliance in the IEQ.

The causes of the increased load are usually easily apparent and therapy obvious. The importance of chest wall stiffness (e.g. pleural thickening) and decreased abdominal compliance (e.g. after abdominal surgery) are sometimes not appreciated. In a patient close to the onset of fatigue, a small reduction of load (e.g. minor bronchodilatation in COPD) can be critical.

Pump capacity. A multitude of factors can impair respiratory muscle pump capacity (tables I, II).

Respiratory muscle weakness has many causes [36], but is most commonly the result of generalized wasting. Wasting and weakness of the respiratory muscles is known to occur in malnourished patients [2], and may also develop in patients mechanically ventilated for prolonged periods, as a consequence of disuse atrophy. The treatment by diaphragm pacing of paralysis secondary to high cervical cord lesions leads to great strengthening of the muscle, suggesting the prior development of profound disuse atrophy [56]. Weakness is also a part of many neuromuscular disorders (e.g. motor neurone disease, myositis, myasthenia gravis), acute [67] and chronic steroid therapy, and metabolic disturbances [6, 7, 15]. Hemidiaphragm paralysis greatly reduces maximum transdiaphragmatic pressures, but is symptomatic only where there is co-existing weakness of other respiratory muscles or pulmonary disease [34]. Respiratory muscle weakness can be a feature of thyroid diseases [43], Addison's disease [44] and the Eaton-Lambert myasthenic syndrome [35].

Hypoxia, if severe, can impair skeletal muscle contractility and potentiate fatigue [28]. Hypercapnic acidosis also impairs limb and respiratory muscle performance [29].

Sepsis, particularly when accompanied by shock, markedly impairs muscle contractility and enhances fatigue [25, 26]. In man, viral upper respiratory tract infections are associated with weakness of the respiratory muscles [45].

Adequate nutrition is crucial to the maintenance of muscle mass and, in the critically ill, parenteral nutrition can increase respiratory muscle strength [30]. It is not yet clear if supplementing the diet of wasted patients with stable chronic lung disease (e.g. COPD) can achieve weight gain, increased respiratory muscle strength and improved ventilatory function [38]. Similarly, the role of respiratory muscle training to increase strength or enhance endurance remains in doubt [57].

Drug therapy to enhance respiratory muscle contractility would appear desirable, and several compounds (particularly the methyl xanthines) increase skeletal muscle performance when administered at high concentrations during *in vitro* studies [3]. Most studies in man have centred around the use of aminophylline and theophylline. Initial reports suggested an important positive inotropic effect of aminophylline on the respiratory muscles [4], but following a large number of studies the benefit of this drug remains a matter for debate [3, 48]. Indeed, there is evidence that aminophylline increases muscle energy consumption and potentiates fatigue [27]. Thus, for the patient poised at the onset of fatigue, a drug which enhances contractility at the expense of excessive energy utilization could hasten respiratory muscle pump failure.

The ideas of acute and chronic respiratory muscle fatigue have provided the rationale for respiratory muscle "rest". In his Amberson lecture to the American Thoracic Society, Dr Peter Macklem proposed that the use of rest therapy could benefit thousands of patients [39]—a sentiment amplified by others [58]. Assisted ventilation, particularly nasal positive pressure ventilation, can "capture" the breathing of patients and may "put the respiratory muscles to rest" [8, 13, 31]. Long term nocturnal domiciliary ventilation can be very successful in the control of ventilatory failure in patients with muscle weakness, kyphoscoliosis and thoracoplasty [63]. This therapy improves day-time arterial oxygen and carbon dioxide tensions and has been reported to improve respiratory muscle strength. The mechanism whereby nocturnal assisted ventilation improves long term day-time blood-gas tensions is not clear. Improved sleep quality, control of cor pulmonale, better matching of ventilation–perfusion, resetting of central respiratory controllers and an increase in lung/chest wall compliance are all possibilities. That such rest relieves fatigue and thereby improves respiratory muscle function is an attractive hypothesis—but pure speculation. The data demonstrating "fatigue" and its reversal by rest are not available. Furthermore, the likelihood that fatigue is an integrated process, and the improbability of the respiratory muscles developing overt fatigue (as analysed above), suggests that rest therapy is unlikely to be beneficial through the mechanism of relief of fatigue. Since persisting reduction in contractility probably does not occur, rest *per se* cannot, therefore, improve contractility.

CONCLUSIONS

At the onset of the fatigue process, central drive is modified to avoid catastrophic force loss or peripheral muscle damage. As it is unlikely that overt high frequency or low frequency fatigue are allowed to develop, it is similarly unlikely that any therapy directed at the treatment of such muscle fatigue (rest or drugs) will be of any value.

The correct therapeutic strategy is a careful evaluation of the three key components of the system: drive, load and capacity. In most circumstances, central respiratory drive will be appropriate and further increases in drive unnecessary and potentially damaging. The crucial balance, therefore, becomes the relationship between respiratory load and respiratory capacity; careful assessment of load and capacity greatly increases our understanding of the patient's problems. Most therapy is directed at reducing load; however, great care must be taken to optimize pump capacity. Unfortunately, the assessment of pump capacity remains rather crude. The impact of respiratory load, in relation to capacity, on respiratory timing and tidal volume provides very useful clinical information.

Further study of respiratory drive, load and capacity will hopefully reveal other clinical parameters, in addition to the rate and depth of breathing, that will allow the identification of patients in danger of the fatiguing process and, therefore, deteriorating ventilatory failure.

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EFFECTS OF ANAESTHESIA ON RESPIRATION

J. F. NUNN

Anaesthesia, with or without paralysis, causes profound changes in respiratory function. There is no question of an overall depression of every facet of the complex matrix of functions which contribute to the oxygenation of the arterial blood; instead, we find highly specific changes, with some aspects of functions markedly affected while others are unaffected. It would have been difficult, if not impossible, to have forecast what is and is not affected by anaesthesia. This has only been elucidated by painstaking research extending back over the past 40 years and with no end in sight.

This work has been greatly limited by our lack of understanding of normal respiratory physiology in the conscious subject. A very important additional problem has been the effect of posture. Most studies of respiratory function in conscious subjects have been undertaken with the subjects in the upright (seated) position, while anaesthesia and intensive care are usually concerned with the supine, prone or lateral decubitus positions. These differences in posture have major effects on respiratory function which are sometimes greater than the effects of anaesthesia itself.

Research in anaesthesia has usually followed closely behind advances in our understanding of respiratory function in the awake subject. Thus technological developments in research have, in general, been applied to anaesthetized patients 2 or 3 years after they have first been used in conscious subjects. This has been the pattern in the case of the measurement of deadspace, the polarographic determination of arterial P_{O_2}, analysis of the distribution of ventilation–perfusion relationships and computed tomography, to cite but a few examples. Either anaesthetists have learned the new technology or, less commonly, basic scientists have been lured into the study of anaesthesia. In both cases there have been formidable practical and ethical problems in the application of new technology to the anaesthetized patient. In many cases ethical constraints have limited the expansion of knowledge, and extrapolation from animal experiments is fraught with difficulty.

EFFECT ON THE PATTERN OF CONTRACTION OF THE RESPIRATORY MUSCLES

It is appropriate to commence with consideration of the effect of anaesthesia on the pattern of contraction of the muscles of ventilation, because it now appears very likely that these changes underlie many of the other changes, such as those in lung volume and pulmonary shunting. However, in this area in particular, our understanding is limited by gaps in our knowledge of what happens in the conscious subject. Furthermore, our knowledge of what happens during anaesthesia is still incomplete and it will be clear that further studies are needed.

The inspiratory muscles

As early as 1857, Snow [51] observed that deepening anaesthesia caused a decrease in thoracic ventilatory excursion. This has been amply confirmed and is usually interpreted as progressive failure of the intercostal muscles, with preservation of the action of the diaphragm. Electromyographic (EMG) confirmation has been obtained in three patients [53] studied first while awake and then during halothane anaesthesia. In the one published pair of records, the intercostal EMG was virtually abolished during anaesthesia, although thoracic expansion (measured as change in antero–posterior diameter) remained surprisingly normal. In contrast to anaesthesia with preserved spontaneous breathing, paralysis and

KEY WORDS

Lung: function, general anaesthesia.

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artificial ventilation cause an increase in the thoracic contribution to total ventilatory excursion from about 25 to 48% [54]. It is therefore remarkable that most indices of distribution of ventilation and perfusion (see below) are much the same during anaesthesia with spontaneous breathing as with artificial ventilation.

There is considerable evidence that the diaphragm retains some tone at the end of expiration in the conscious subject in the supine, although probably not in the upright, position. Residual diaphragmatic EMG activity has been demonstrated in a single supine patient while conscious, but not while anaesthetized with halothane [38].

If there is indeed end-expiratory diaphragmatic tone in the supine position, and this is abolished by anaesthesia, it would seem to provide a very plausible explanation of the cephalad excursion of the diaphragm which has been reported to follow the induction of anaesthesia. However, it must be stressed that the often-cited radiological study of Froese and Bryan [20] reported changes in the position of the diaphragm at functional residual capacity (FRC) in only two subjects. In each subject, anaesthesia without paralysis produced changes virtually identical to those of paralysis without anaesthesia. In one patient (illustrated in their figure 1) the end-expiratory position of all parts of the diaphragm moved cephalad by a mean distance of about 2.5 cm. However, in the other patient, the posterior part of the diaphragm moved cephalad while the anterior part moved caudad by approximately the same distance, the mean change being close to zero.

Computed tomography has been used in six patients to demonstrate a mean cephalad movement in the end-expiratory position of the diaphragm following induction of anaesthesia of 1.9 cm, which was calculated to result in a decrease of thoracic volume of 500 ml [22]. However, for the control awake end-expiratory exposures, it was necessary for subjects to hold the breath voluntarily in the end-expiratory position for 5 s with their arms above their heads. The movement of the diaphragm was determined from scout frontal images [Hedenstierna, personal communication].

Dynamic spatial reconstruction of the diaphragm has been used in six volunteers (three supine, three prone) to determine the effect of anaesthesia–paralysis [32]. Of the three supine subjects, two showed a net *cephalad* displacement corresponding to 124 and 196 ml, respectively, while the third showed a *caudad* movement of 73 ml. In contrast, the three subjects in the prone position showed a consistent cephalad movement with a mean volume change of 615 ml after induction of anaesthesia–paralysis.

Thus there remains a measure of disagreement about the effects of anaesthesia and paralysis on the end-expiratory position of the diaphragm and it is evident that there is substantial individual variation. The relevance to change in FRC is considered below.

The expiratory muscles

General anaesthesia with preserved spontaneous breathing usually causes phasic activity of the expiratory abdominal muscles, which are normally silent in the conscious supine subject [19, 27]. This would be no surprise to the older generation of surgeons, but otherwise it seems to have no functional significance [24].

Other muscles

EMG activity has been reported during inspiration in the genioglossus muscle in sleeping obese patients [48] and in awake subjects particularly during nasal breathing [3]. Conversely, only tonic activity of genioglossus was found in another study of patients before induction of anaesthesia [13]. In the cat, there is interference with hypoglossal nerve activity during anaesthesia [40] and the tongue moves posteriorly during anaesthesia in man, although not usually occluding

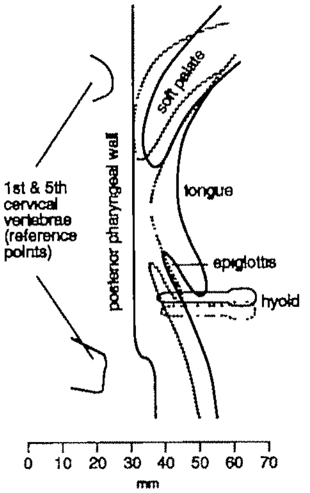

soft palate
1st & 5th cervical vertebrae (reference points)
posterior pharyngeal wall
tongue
epiglottis
hyoid
0
10
20
30
40
50
60
70
mm

FIG. 1. Changes in the geometry of the pharynx in the medial sagittal plane following the induction of anaesthesia. —— = Awake; —— = anaesthetized. (Drawn from data in reference [39].)

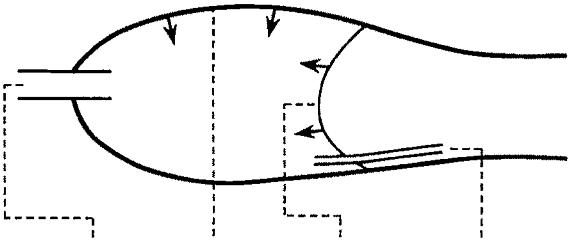
the oropharynx [37, 39]. In addition, the soft palate moves posteriorly, closing the nasopharynx in almost all patients (fig. 1) and Drummond has reported further complex changes in the sternothyroid, sternohyoid and scalene muscles [13]. The epiglottis moves posteriorly without downfolding, but does not touch the posterior pharyngeal wall in most patients. It has been suggested, however, that this is the major site of interference with the pharyngeal airway [10].

CHANGE IN FUNCTIONAL RESIDUAL CAPACITY

With the subject in the supine position, FRC is about 1 litre less than in the upright position. There is widespread agreement that a further decrease of approximately 450 ml (or about 18 %) occurs after the induction of anaesthesia with all drugs which have been investigated to date [41]. The decrease occurs immediately after induction, is not progressive and is not related to the inhalation of high concentrations of oxygen. FRC is reduced by the same amount whether the patient is paralysed or not, and expiratory muscle activity has no significant effect [24]. The reduction in FRC has a weak but significant correlation with the age of the patient. Artificial ventilation of the conscious subject causes only a small reduction in FRC and anaesthesia does not change FRC in the sitting position [50].

Cause of the change in FRC

Possible causes include cephalad movement of the diaphragm, decrease in the cross-sectional area of the rib cage and movement of blood into or out of the thorax. There is currently disagreement as to the magnitude of all these changes between groups working in the Karolinska Hospital, Stockholm [22] and the Mayo Clinic [31, 32]. These differences are summarized in figure 2. Many factors contribute to the difficulty in resolving this problem. Radiation dosage and other difficulties have generally restricted the number of subjects to less than that required for satisfactory statistical resolution of the great individual variations which appear to exist. Furthermore the measurement techniques are not directly comparable, and there are other differences in the circumstances of the studies. Drummond [14] has not found any shifts in central blood volume following induction of anaesthesia. The only area of agreement is in the magnitude of the change in FRC. It should be stressed that FRC has usually been studied during anaesthesia with a tracheal tube in place. It has been reported that methohexitone reduces FRC by the expected amount only when a tracheal tube is in place, but not when a face mask is used [8].



Decrease in FRC		Decrease in rib cage volume		Cephalad movement of diaphragm		Movement of blood
450	=	250	+	500	-	300 (out of thorax)
590	=	170	+	110	+	310 (into thorax)

Volume changes after induction of anaesthesia (ml)

FIG. 2. Data on changes in functional residual capacity (FRC) and thoracoabdominal dimensions according to two sources [22, 31].

Consequences of the change in FRC

In the supine position, the mean value of the FRC of the conscious subject is only about 2 litre. Induction of anaesthesia will further reduce FRC until it is close to the residual volume. This has major effects on lung function, particularly in respect to airway calibre, airway closure, pulmonary collapse, compliance and gas exchange.

Airway calibre. Changes in lung volume affect all components of the tracheobronchial tree and have a direct effect on airway calibre, particularly in the dependent parts of the lung. However, this effect is largely offset by the bronchodilator effect of the common inhalation anaesthetics. As a result, there is usually no major change in airway resistance following induction of uneventful anaesthesia.

Nevertheless, there are many abnormal causes of increased airway resistance which may arise during anaesthesia and which may be serious. For example, excessive resistance or even total obstruction may arise in apparatus such as breathing systems, valves, connectors and tracheal tubes. The pharynx is usually at least partially obstructed as described above. The large airways may be blocked with foreign material such as blood, tumour, pus or inhaled gastric contents.

Bronchospasm may result from many causes. Factors influencing airway calibre have been further reviewed in this issue [25].

Airway closure. The reduced FRC during anaesthesia in the supine position will often be less than closing capacity (CC), at least in older patients. This would be expected to result in airway closure, collapse in dependent parts of the lung, shunting and arterial hypoxaemia. These changes can very easily be demonstrated in older subjects who breathe at reduced lung volume in the supine position [43].

Airway closure would not occur during anaesthesia if CC were to decrease by the same amount as FRC, as has been suggested [7, 26]. Nevertheless, the demonstration of collapse in dependent areas of lung during anaesthesia (see below) strongly suggests that airway closure does, in fact, occur during anaesthesia. Furthermore, it has been shown that, during anaesthesia, there is a very strong relationship between shunt and (FRC (anaesthesia) – CC (preanaesthesia))/total lung capacity [15]. This would appear to indicate that the shunt seen during anaesthesia is indeed related to the change in FRC, and airway closure is the likely cause.

Pulmonary collapse. In 1963, Bendixen, Hedley-Whyte and Laver [5] suggested that some degree of pulmonary collapse is a normal feature of anaesthesia. A series of later studies failed to confirm this, and collapse was never demonstrated by conventional radiography, except in the dependent lung in the lateral position. However, "compression atelectasis" in dependent lung areas following induction of anaesthesia has now been demonstrated unequivocally by computed tomography [11, 21, 52]. Such areas of collapse form rapidly, always in the dependent part of the lungs, and tend to disappear with positive end-expiratory pressure. The area of collapse correlates strongly with the shunt (see below).

Compliance. In addition to the reduction in FRC and expiratory reserve already described, anaesthesia results in a reduction of total lung capacity and total compliance [41, 55]. The major component of the change in compliance is in the lung rather than the chest wall, and many authors have shown that pulmonary compliance is approximately halved after the induction of anaesthesia. Below FRC, total compliance is particularly low since, during anaesthesia, the expiratory reserve volume is only a few hundred millilitres at best, and may be zero. Therefore effective pulmonary ventilation cannot usually be achieved during anaesthesia by application of intermittent sub-atmospheric pressure, or by external thoracic compression. Although there are major differences in compliance between the conscious state and anaesthesia, there are only minor differences between anaesthesia with and without paralysis [55].

The cause of the reduction in pulmonary compliance is not immediately obvious. There is no general agreement on the effect of anaesthetics on the pulmonary surfactant and the reduced compliance may well be secondary to the reduced FRC or altered pattern of tidal expansion of the chest wall. A reduction in pulmonary compliance is known to result from restrictive strapping of the rib cage. Respiratory mechanics have been further reviewed in this issue [35].

CONTROL OF BREATHING

Pulmonary ventilation is usually decreased during anaesthesia with preserved spontaneous breathing. In part this reflects the reduction in metabolic rate (see below) but, in addition, it results from a number of highly specific effects of anaesthesia upon the various mechanisms which control breathing.

Effect on $P\text{CO}_2$*–ventilation response curve*

It has long been known that the $P\text{CO}_2$–ventilation response curve is depressed by anaesthetics in a dose dependent manner (fig. 3). There are no striking differences between the halogenated volatile anaesthetics, and the ventilatory response to carbon dioxide is probably abolished at about twice the minimal alveolar concentration required for anaesthesia (i.e. 2 MAC). Diethyl ether has little effect at 1 MAC, possibly because of release of catecholamines. There are obvious difficulties in studying the effect of nitrous oxide at comparable MAC multiples, but it is well established that partial replacement of a volatile halogenated anaesthetic with the same MAC fraction of nitrous oxide (usually 0.5–0.7) results in increased pulmonary ventilation and decreased $P\text{CO}_2$ [17]. This suggests that nitrous oxide has an effect more like diethyl ether than the volatile halogenated anaesthetics. Surgical stimulation antagonizes the effect of

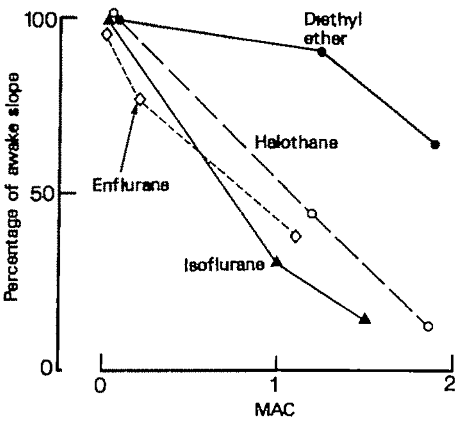


FIG. 3. The slope of $P\text{CO}_2$–ventilation response curves as a function of multiples of the minimal alveolar concentration (MAC) required for anaesthesia for different anaesthetics. (Reproduced from reference [41], with the permission of the publishers.)

anaesthesia on the $P\text{CO}_2$–ventilation response curve and there is no evidence of significant progressive increase in $P\text{CO}_2$ when anaesthesia is maintained at constant depth during surgery [1].

The effect of anaesthetics on the $P\text{CO}_2$–ventilation response curve was originally thought to be exerted in the medulla, but it has been suggested that the increase in ventilation attributable to increased $P\text{CO}_2$ is largely attributable to the intercostal muscles which have been shown to be selectively inactivated during anaesthesia [53]. Thus the effect may well depend at least in part on the effect of anaesthetics on the pattern of contraction of the inspiratory muscles.

Extrapolation of the $P\text{CO}_2$–ventilation response curve to the axis of zero ventilation indicates the apnoeic threshold for $P\text{CO}_2$. Conscious subjects do not necessarily stop breathing when their $P\text{CO}_2$ is less than the apnoeic threshold; however, during anaesthesia, patients almost invariably become apnoeic when $P\text{CO}_2$ is less than the apnoeic threshold value.

Effect on PO_2*–ventilation response curve*

The hypoxic ventilatory response is extremely sensitive to inhalation anaesthetics, even at 0.1 MAC [30] and it appears that the effect is on the carotid body chemoreceptor itself [12, 28]. It should be emphasized that there are ethical constraints in studying any effect of hypoxia in patients. Therefore, the subjects for human studies of the effects of anaesthesia on the $P\text{O}_2$–ventilation response curve have been the investigators themselves. Consequently, numbers are limited and the full extent of individual variation has not been explored.

There are some important consequences of this effect which must be presumed to continue into the postoperative period, until the alveolar concentration of the anaesthetic has declined well below that which causes loss of consciousness. First, the patient cannot act as his own hypoxia alarm by responding with hyperventilation. Second, the patient who has already lost his sensitivity to $P\text{CO}_2$ (e.g. "the blue bloater") may stop breathing after anaesthesia has abolished his hypoxic drive. Finally, anaesthesia may be dangerous at very high altitude or in other situations where survival depends on hyperventilation in response to hypoxia [42].

Response to metabolic acidaemia

The ventilatory response to metabolic acidaemia also is obtunded by anaesthesia, and even by subanaesthetic concentrations of anaesthetics [29].

Response to added resistance

Anaesthetics have such profound and deleterious effects on the chemical control of breathing that it is surprising to find that the ability of a patient to increase his work of breathing in response to added resistance is remarkably well preserved [36, 44]. The anaesthetized patient responds to inspiratory loading by two mechanisms, one of which appears to be reflex and the other the result of an increased $P\text{CO}_2$. The first is instantaneous and occurs during the first loaded breath. The second takes several minutes to develop and results in hyperventilation when the resistance is removed. This provides a very sensitive test of excess respiratory resistance.

Anaesthetics and pulmonary stretch receptors

The common inhalation anaesthetics, particularly trichloroethylene, sensitize the pulmonary stretch receptors in cats, but this is unlikely to be the full explanation of the increase in the rate of ventilation in man in whom the Hering–Breuer reflex is virtually absent.

METABOLIC RATE

The metabolic rate during anaesthesia is about 15% less than basal according to the conventional standards, which do not stipulate sedation or any period of rest. A similar reduction in metabolic rate follows 3 h of rest, with or without sedation [49]. The sub-basal metabolic rate during anaesthesia mitigates, to some extent, the adverse effects of anaesthesia upon gas exchange. However, dramatic increases in metabolic rate may occur during hyperthermia, shivering or convulsions.

PULMONARY VENTILATION

During anaesthesia with artificial ventilation, the minute volume can be set at almost any value which seems appropriate to the anaesthetist. Hyperventilation is usual and values up to 15 litre min^{-1} are commonplace, with arterial $P\text{CO}_2$ ranging from normal down to about 2.5 kPa. It has proved difficult to demonstrate that this does any significant harm to the healthy patient, although there is obvious concern for the cerebral circulation.

If spontaneous breathing is preserved during anaesthesia, the minute volume may remain normal but is usually decreased because of interference with the control of breathing and the function of the respiratory muscles as described above. Sometimes the minute volume reaches very low values, and as little as 3 litre min^{-1} has been recorded, with corresponding $P\text{CO}_2$ values up to about 10 kPa [1]. This is particularly likely to occur in the absence of surgical stimulation. There are no outcome studies to indicate that this is harmful to a healthy patient.

EFFECT ON HYPOXIC PULMONARY VASOCONSTRICTION (HPV)

All inhalation (but not i.v.) anaesthetics inhibit HPV by a mechanism which is still unclear. A typical sigmoid dose–response curve has been demonstrated, with an ED_{50} of slightly less than 2 MAC and an ED_{90} of about 3 MAC [33]. However, most anaesthetics also decrease cardiac output and consequently mixed venous $P\text{O}_2$, which is an important component in HPV. It is now clear that inhalation anaesthetics depress HPV in a predictable manner, provided that allowance is made for changes in cardiac output [34].

Interference with HPV is an important factor increasing pulmonary blood flow through underventilated and therefore hypoxic areas of the lung during inhalation anaesthesia. Similarly in one-lung anaesthesia, inhalation anaesthetics cause a small but definite increase in the flow through the collapsed lung [6]. HPV is discussed in greater detail elsewhere in this issue [18].

DISTRIBUTION

Regional ventilation and perfusion of the lung are normally fairly well matched in the conscious supine subject. However, even during uncomplicated anaesthesia, the changes in lung volume, altered geographical distribution of inspired gas and interference with HPV, as described above, all contribute to abnormalities of the relative distribution of ventilation and perfusion, except in some very young and fit patients. These changes do not normally pose any major threat to the patient. Any tendency to hypoxaemia can normally be counteracted by increasing the oxygen concentration in the inspired gas. However, such "normal" changes may be contrasted with a more serious range of pathological alterations in distribution as a result of such causes as bronchial intubation, tension pneumothorax, gross hypotension or the combination of respiratory disease with anaesthesia. Under such conditions, maldistribution may be a potent cause of mortality and morbidity.

Although there is a continuous gradation of ventilation/perfusion ratios ($\dot{V}/\dot{Q}$) in different alveoli, it is often convenient and practical to consider the lung as a three-compartment model. In this model the alveoli are considered as though they fall into three groups: "ideally" ventilated and perfused alveoli, unperfused alveoli (alveolar deadspace or infinite $\dot{V}/\dot{Q}$ ratio) and unventilated alveoli (shunt or zero $\dot{V}/\dot{Q}$ ratios). In fact, almost any combination of abnormalities in the distribution of ventilation and perfusion can be represented *as if* the arterial $P\text{O}_2$ and $P\text{CO}_2$ were influenced by increased deadspace, shunt, or both.

The advantages of this approach are twofold. First, the equipment for making the relevant measurements is available in any department of anaesthesia which operates a blood-gas electrode system. Second, the results provide clear guidance for making physiological correction for the abnormality.

Deadspace

It is now well established that the alveolar component of the physiological deadspace is increased during anaesthesia. Thus the physiological deadspace (measured by entering the arterial $P\text{CO}_2$ into the Bohr equation) normally exceeds the anatomical deadspace (the volume of the conducting air passages) [45]. During anaesthesia, the physiological deadspace/tidal volume ratio from carina downwards averages 32%, with either spontaneous or artificial ventilation, and over a wide range of tidal volume. The relationship still applies during hypoventilation when the anatomical deadspace is reduced in proportion to the tidal volume, presumably because of streamline gas flow and cardiac mixing of sub-carinal gas.

In practice, the apparatus deadspace of the tracheal tube (or face mask) and its connections must be added for the purpose of calculating alveolar ventilation during anaesthesia. As a rough guide, the total deadspace is then about 50% of the tidal volume with a tracheal tube, and 67% of the tidal volume with a mask.

Compensation for increased deadspace during artificial ventilation may be made by increasing the minute volume to maintain the required value for alveolar ventilation. In the case of the hypoventilating patient (usually breathing spontaneously), the reduction in the absolute volume of all components of the deadspace offsets much of the expected diminution in alveolar ventilation.

The cause of the increased alveolar deadspace is not entirely clear. It seems unlikely that it results from pulmonary arterial hypotension causing failure of perfusion of non-dependent alveoli (Zone 1 conditions). The alternative explanation is ventilation of alveoli with high (but not infinite) $\dot{V}/\dot{Q}$ ratios. Some of the studies of $\dot{V}/\dot{Q}$ distribution described below do show such changes, but they are by no means consistently present during uncomplicated anaesthesia.

Shunt

It is a consistent finding that, during anaesthesia, the alveolar–arterial $P\text{O}_2$ difference is increased to a value which corresponds to a shunt of about 10% [41]. This provides an acceptable basis for calculating the concentration of oxygen in the inspired gas which will provide an acceptable arterial $P\text{O}_2$ during anaesthesia, and this is usually in the range 30–40%.

There now seems little doubt that the shunt is caused by compression collapse of the lung [21, 23]. The development of shunt during anaesthesia has now been related clearly to the decrease in lung volume [15], and it seems likely that decrease in lung volume causes lung collapse which, in turn, is the main cause of the increase in shunt.

Ventilation/perfusion ($\dot{V}/\dot{Q}$) relationships

The distribution of pulmonary ventilation and perfusion in relation to $\dot{V}/\dot{Q}$ ratios may now be studied by means of the inert gas wash-out technique. In young fit subjects, it was found that both ventilation and perfusion were distributed to a somewhat wider range of $\dot{V}/\dot{Q}$ ratios after induction of anaesthesia and paralysis, but that true intrapulmonary shunt had a mean value of less than 1% during anaesthesia [47].

Older surgical patients have been studied while awake, anaesthetized and breathing spontaneously, anaesthetized–paralysed and ventilated artificially, and with PEEP [9]. True intrapulmonary shunt was increased during anaesthesia, but not sufficiently to account for the increased alveolar–arterial $P\text{O}_2$ gradient, the difference being attributable to perfusion of areas of low $\dot{V}/\dot{Q}$ ratio. The deadspace/tidal volume ratio was increased during anaesthesia in spite of the tracheal tube bypassing the upper airway. PEEP reduced the shunt, but also reduced the cardiac output and therefore the mixed venous oxygen content. The decreased admixture of more desaturated blood resulted in virtually no change in arterial $P\text{O}_2$. In elderly patients who all had some deterioration in pulmonary function, large increases in true shunt and in perfusion of regions of very low $\dot{V}/\dot{Q}$ ratios were found during anaesthesia [16].

These studies confirm that the major changes can indeed be considered in terms of the three-compartment model and also emphasize the importance of the age of the patient, particularly in respect of increase in the alveolar–arterial $P\text{O}_2$ gradient. The increase in alveolar deadspace appears to be the result of increased distribution of ventilation to areas of high (but not usually infinite) $\dot{V}/\dot{Q}$ ratios. It is now amply confirmed that the major differences are between the awake and the anaesthetized states. Paralysis and artificial ventilation do not greatly alter the parameters of gas exchange, in spite of the quite different spatial distribution of ventilation. Finally, we may now be clear that, although PEEP reduces the shunt, the beneficial effect on arterial $P\text{O}_2$ is offset by the decrease in cardiac output which reduces the mixed venous oxygen content.

THE POSTOPERATIVE PERIOD

Increased $P\text{CO}_2$ and increased alveolar–arterial $P\text{O}_2$ gradient return to normal during the first few hours after minor operations [46]. However, the early stages of elimination of nitrous oxide in the first few minutes of recovery may dilute the alveolar gas and so reduce both $P\text{CO}_2$ and $P\text{O}_2$. This is only a transient effect and any tendency towards hypoxaemia can be avoided by allowing the patient to breathe oxygen for a few minutes.

The normal pattern of recovery may be altered by shivering in the early postoperative period, which causes a large increase in oxygen consumption, requiring a corresponding increase in minute volume [4]. Following major surgery there may be residual shunting through areas of pulmonary collapse and restoration of a normal alveolar–arterial $P\text{O}_2$ gradient may take a few days [2]. This is associated with a continued reduction in FRC.

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EFFECTS OF ANAESTHETICS ON THE PULMONARY CIRCULATION

J. B. EISENKRAFT

It is well established that general anaesthesia may impair gas exchange in the lung and that arterial hypoxaemia may occur as a result. Nunn [46] investigated the factors which influence the arterial oxygen tension (Pa_{O_2}) during halothane anaesthesia (1.0–1.5 %) during spontaneous ventilation. He reported a calculated shunt of 14 % of total pulmonary blood flow, as compared with a calculated shunt of only 1 % in normal conscious supine subjects in whom the same measurement techniques had been used [47]. Nunn suggested that the large shunt found during anaesthesia was probably caused by increased perfusion of totally unventilated parts of the lung, and that maldistribution of ventilation:perfusion ratios caused that part of the total alveolar–arterial P_{O_2} difference which could not be accounted for by shunt. Thus regions of low ventilation:perfusion ratio, which have little effect on elimination of carbon dioxide, cause a marked impairment of oxygenation of the arterial blood [46].

Marshall and colleagues [34] studied pulmonary venous admixture before, during and after halothane in oxygen anaesthesia in 10 spontaneously breathing patients. The mean inspired tension of halothane was 0.8–1.1 kPa (approximately 0.9 %). The percentage pulmonary venous admixture (Qs/Qt %) was 4.4 % before anaesthesia, increasing to 12.1 % and 14.8 % at 40 min and 3 h of anaesthesia respectively, and 6.5 % and 5.2 % at 40 min and at 3 h after anaesthesia. These authors [34] concurred essentially with Nunn [46] and also concluded that, in their study, the postoperative hypoxaemia observed was the result, not of respiratory depression, but of residual effects of increased venous admixture which had developed during the anaesthetic.

All patients undergoing general anaesthesia show changes in lung mechanics, such as decreases in compliance and functional residual capacity, as well as changes in the distribution of ventilation [49]. Although these changes may contribute to the observed impairment of oxygenation, they do not provide a complete explanation, because similar changes in mechanics occur with both inhaled and i.v. anaesthetic drugs, yet inefficient oxygen exchange has been established only with the inhaled agents [35]. This suggests that inhaled agents exert a specific effect which tends to produce hypoxaemia. Interest has therefore been directed to the regulation of the pulmonary circulation during anaesthesia, and in particular to hypoxic pulmonary vasoconstriction (HPV). This is a homeostatic mechanism by which pulmonary blood flow is diverted away from hypoxic areas, thereby optimizing gas exchange.

NORMAL MECHANISM OF HYPOXIC PULMONARY VASOCONSTRICTION

Hypoxic pulmonary vasoconstriction was described first in 1942 by Von Euler and Liljestrand [68], investigating pulmonary haemodynamic responses in the cat to changes in the inspired gas composition. Cats were anaesthetized with i.v. chloralose; systemic arterial pressure was measured from one carotid artery, while pulmonary arterial pressure was recorded via a cannula inserted directly into the pulmonary artery. The cats were studied during both spontaneous and positive pressure breathing. It was found that when they breathed an FI_{O_2} of 0.105 (10.5 % oxygen in nitrogen), the pulmonary arterial press-

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ure invariably increased. Neither vagotomy nor stellate ganglionectomy influenced this response, which was thought to be a direct effect of hypoxia on the pulmonary vasculature. At $F\text{I}_{O_2}$ 1.0, pulmonary arterial pressure decreased. The authors concluded that the increase in pulmonary arterial pressure during hypoxia was the result of a direct effect on lung vessels, "thereby increasing the blood flow to better aerated lung areas which leads to improved conditions for the utilization of the alveolar air" [68].

While in the classic study of Von Euler and Liljestrand both lungs were rendered hypoxic, others have studied the effect of the size of the lung segment made hypoxic and the severity of the hypoxic stimulus on perfusion pressure and flow diversion. In one such study, six mongrel dogs were anaesthetized with pentobarbitone and electromagnetic flow probes were placed around the main, left and left-lower lobe pulmonary arteries [38]. Pressures were measured in the main pulmonary artery, left atrium and abdominal aorta. Following insertion of a Robertshaw left-sided bronchial tube, and a left lower lobe bronchotomy whereby a separate tube was placed to permit independent ventilation of the left lower lobe, ventilation of different sized segments of lung could be achieved [38].

The effects of changing $F\text{I}_{O_2}$ were observed in test lung segments of seven different sizes which corresponded to left lower lobe, upper lobe lingula, left lung, right lung, right lung plus left lower lobe, right lung plus left upper lobe lingula, and whole lung. In each experiment, the rest of the lung was ventilated with an $F\text{I}_{O_2}$ of 1.0, while HPV in the test segment was demonstrated by both increased perfusion pressure (mean pulmonary arterial pressure minus mean left atrial pressure) and diversion of blood flow away from the hypoxic test segment. It was found that changes in pulmonary perfusion pressure increased with the size of the hypoxic lung segment from 0 (smallest hypoxic segment) to approximately 2.2 times baseline when the whole lung was rendered hypoxic. The diversion of flow, as a percentage of the blood flow to the test segment under normoxic conditions, decreased as the size of the hypoxic segment increased. Flow diversion increased linearly as $P\text{a}_{O_2}$ decreased in the range 17.3–3.7 kPa. In terms of both flow diversion and changes in perfusion pressure, the HPV response was predictable, continuous, and maximal at a predicted $P\text{a}_{O_2}$ of 4.0 kPa [38]. Thus the HPV response caused an increase in perfusion pressure and blood flow diversion.

Site for stimulation of HPV and its sensitivity

Characteristics of the stimulus site for HPV have been studied *in vitro* using an isolated rat lung preparation [41]. The lungs were perfused and ventilated with separate control of $P\text{A}_{O_2}$ and $P\bar{\text{v}}_{O_2}$. The lungs were perfused with blood from donor rats and, with perfusion flow kept constant, HPV was measured as a change in perfusion pressure. Both the perfusate and the ventilating gas concentrations were varied between $F\text{I}_{O_2}$ values of 0.00 and 0.21 while the HPV responses were measured. In this study HPV was found to be a function of both $P\text{A}_{O_2}$ and $P\bar{\text{v}}_{O_2}$ and the relationship could be expressed as if the two combined to give a single oxygen tension ($P\text{s}_{O_2}$) at the HPV stimulus site [41]. The relationship could be expressed mathematically as:

$$P\text{s}_{O_2} = [(P\text{A}_{O_2})^{0.62} \times (P\bar{\text{v}}_{O_2})^{0.38}]$$

The $P\text{s}_{O_2}$–HPV response curve was sigmoid, with a 50% response when both $P\text{A}_{O_2}$ and $P\bar{\text{v}}_{O_2}$ were 4.04 kPa, at which point $P\text{s}_{O_2}$ was also 4.04 kPa. It was concluded also that $P\text{A}_{O_2}$ had a greater effect than $P\bar{\text{v}}_{O_2}$ as a result of oxygen exchange between gas in the alveoli and blood in small pulmonary arteries [41].

Atelectasis and HPV

Under normal circumstances, when a lung is made atelectatic, blood flow to that lung is decreased. The relative contribution of passive mechanical forces *vs* HPV as mechanisms for reducing blood flow in atelectatic lung were studied in a dog model [1]. Selective atelectasis of the left lower lobe caused lobar blood flow (measured using an electromagnetic flow probe) to decrease 59% from control. Re-expansion and ventilation of the left lower lobe with a mixture of 95% nitrogen in carbon dioxide, which would terminate any mechanical effect, resulted in no significant increase in lobar flow. Ventilation of the lobe with 100% oxygen, which would terminate any stimulation of HPV, increased lobar blood flow to control values. It was therefore concluded that the major mechanism whereby blood flow to atelectatic lung is decreased is HPV [1]. A similar conclusion was reached by Miller and colleagues [43], who studied an anaesthetized, open-chest dog model in which the whole left lung was made atelectatic. In this study left lung blood flow during hyperoxic conditions was calculated by multiplying cardiac output by the fractional carbon dioxide excretion from the left lung. Left lung blood flow during hypoxic ventilation or atelectasis was calculated from blood oxygen contents using a blood mixing equation [43].

In those regions of the lung that are atelectatic, the stimulus for HPV is the $P\bar{v}_{O_2}$. In a study using intact dogs, Domino and colleagues [26] found that the blood flow reduction observed in atelectatic lung was a function of $P\bar{v}_{O_2}$. Approximately 50% of blood flow was diverted away from atelectatic lung when $P\bar{v}_{O_2}$ was low (3.2 kPa) or normal (6.1 kPa). When $P\bar{v}_{O_2}$ exceeded 13.3 kPa, blood flow was not diverted away from atelectatic lung and lung blood flow was nearly that expected under normoxic conditions. The authors also concluded that the contribution of mechanical factors in reducing blood flow to atelectatic lung in the open chest situation was small [26].

The exact mechanism of the HPV response remains to be determined, but it is believed to be accounted for by each smooth muscle cell in the pulmonary arterial wall responding to the oxygen tension in its vicinity [41]. It has been observed that the smooth muscle in the pulmonary arterial wall depolarizes and develops spontaneous electrical activity in response to hypoxia and other contractile stimuli [28, 31]. Increased calcium channel activity may be important in the mechanism of HPV because BAY K8644, a Ca^{2+}-channel potentiator, enhances HPV, while nifedipine diminishes it [66]. Other studies have been directed towards determining whether HPV occurs mainly in alveolar or extra-alveolar vessels. The results suggest that the site of HPV varies among species, but is predominantly observed in precapillary arteries [16].

Effect of HPV on arterial oxygenation

Hypoxic pulmonary vasoconstriction can have a significant effect on Pa_{O_2}. If flow diversion occurs when part of a lung is made hypoxic, Pa_{O_2} should be greater than if there were no HPV. The relationship between Pa_{O_2} and the amount of lung

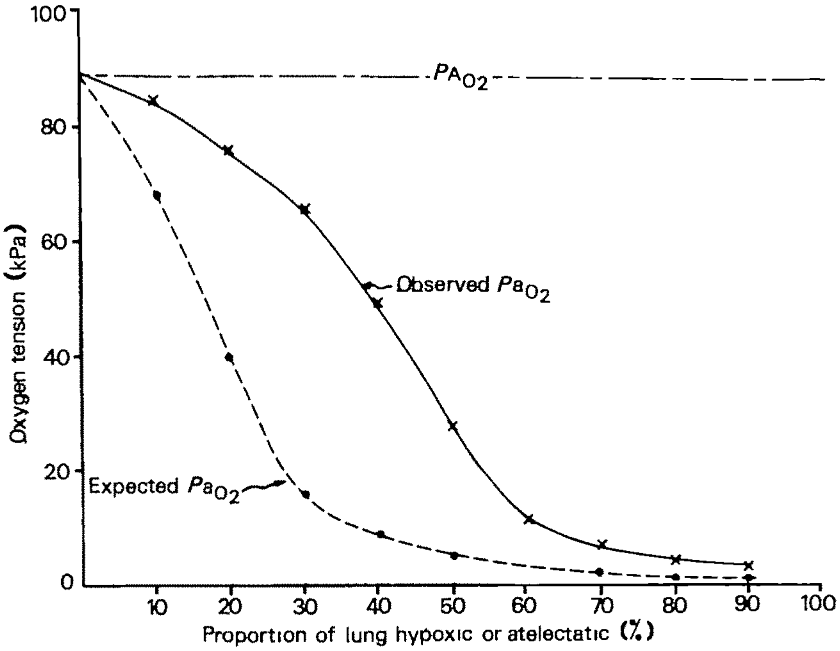

FIG. 1. Role of hypoxic pulmonary vasoconstriction (HPV) in preserving arterial oxygen tension (Pa_{O_2}) in dogs, assuming Pa_{CO_2} = 5.33 kPa, ($Ca_{O_2} - C\bar{v}_{O_2}$) = 5 ml dl^{-1} and haemoglobin = 14 g dl^{-1}. Lung is ventilated with 100% oxygen while increasing proportions of lung are subjected to hypoxia or atelectasis. In the absence of HPV the expected Pa_{O_2} would follow the dashed line, whereas in the presence of an active HPV response the observed Pa_{O_2} is maintained closer to the solid line. (Adapted from [38] by permission of the American Physiological Society and the author.)

tissue made hypoxic (fig. 1) shows that, when little of the lung is hypoxic, HPV has little effect on Pa_{O_2} because in this situation the shunt is small [2, 36, 37]. If most of the lung is hypoxic, effective flow diversion is not possible and it becomes irrelevant, in terms of Pa_{O_2}, whether the hypoxic lung region has HPV or not. In the latter case active HPV would, however, increase pulmonary vascular resistance and thereby increase the work of an already hypoxic heart [2].

When the amount of lung tissue made hypoxic is intermediate, there may be a large difference between the Pa_{O_2} expected with normal HPV compared with that in its absence. Such a situation may exist during one-lung anaesthesia for thoracic surgery, when an active HPV response can increase Pa_{O_2} from potentially dangerously low arrhythmogenic values to higher and safer ones. Thus, during studies of one-lung ventilation, shunt through the non-ventilated lung is usually about 25% of the cardiac output, in contrast to the 40–50% which might be expected if blood flow to the collapsed lung continued as if to a ventilated lung [2].

This brief overview of normal HPV has demonstrated the value of this homeostatic mechanism and how impairment of it may result in arterial hypoxaemia.

EFFECTS OF ANAESTHETICS ON HPV

The effects of anaesthetic agents on HPV were first described by Buckley and colleagues [17]. Using a dog model they found that nitrous oxide increased the HPV response, but that 0.5% halothane, which had no significant effect on cardiac output, abolished HPV [17]. There have been many subsequent studies of the effects of anaesthetics on HPV. All manner of ingenious preparations, methods and species have been used and the results have frequently been inconsistent. Benumof [2] has classified the preparations used for these studies as *in vitro*, *in vivo* non-intact, *in vivo* intact, and human studies. This useful classification will be followed here.

Inhaled Anaesthetic Agents

In vitro *preparations*

The first extensive studies of the effects of inhaled agents on HPV were by Sykes and colleagues [59, 63]. They studied isolated cat and dog lung preparations perfused at constant flow using a special perfusion circuit and ventilated with either normoxic or hypoxic gas mixtures. They found that the pressor response to hypoxaemia could be elicited for up to 5 h and that it was inhibited by halothane, trichloroethylene and diethyl ether added to the inhaled gas mixture.

Similar results were found by Bjertnaes [10], who perfused isolated rat lungs with blood at a constant volume pulsatile inflow and used change in inflow pressure as a measure of HPV. In this study, the lungs were ventilated with normoxic and hypoxic gas mixtures, with and without potent inhaled agents. The results showed a dose-related reversible inhibition of HPV with diethyl ether, halothane and methoxyflurane [10].

Marshall, Lindgren and Marshall [40] used a similar isolated rat lung model to study the effects of halothane, enflurane and isoflurane on HPV. All three agents were found to depress HPV in a dose-related manner. The concentrations in MAC units (adjusted for rats) at which a 50% inhibition of HPV occurred (the ED_{50}) were 0.47, 0.60 and 0.56 for halothane, isoflurane and enflurane, respectively, and neither the ED values nor the slopes of the dose–response curves were significantly different among the agents. It was therefore concluded that they inhibit HPV with essentially identical potencies.

An isolated rat lung preparation has also been used to study the effects of potent inhaled agents on the vascular resistance in atelectatic lungs [15]. Two pairs of isolated rat lungs were perfused in series at constant flow. One preparation was made atelectatic by airway occlusion, while ventilation of the other preparation using a hypoxic mixture (2% oxygen) resulted in an increase in vascular resistance in both preparations. Administration of halothane, enflurane or ether to the atelectatic lung via the ventilated preparation caused a dose-dependent reversible reduction of vascular resistance. The same reduction in resistance occurred when the perfusate P_{O_2} was increased. Thus halothane, enflurane and ether reduced the vascular resistance in the isolated perfused hypoxic atelectatic lung [15].

In all of the above studies [10, 15, 40, 59, 63], HPV was measured as a change in perfusion pressure during constant flow, and hypoxia was induced and the potent agent introduced by ventilation of the isolated perfused lungs.

In vivo *non-intact preparations*

The effects of inhaled anaesthetic agents (isoflurane, fluroxene, halothane, nitrous oxide) were studied in a dog model in which the left lower lobe had been isolated for separate ventilation [5]. Electromagnetic flow probes were placed around the main and left lower lobe pulmonary arteries, and the pulmonary arterial and left atrial pressures were measured directly. The limitations of flow meters have been discussed elsewhere [53]; in particular, to have good contact between probe and vessel, the probe must constrict the vessel, thereby decreasing its conductance and potentially altering both flow distribution and perfusion pressure of the lobe under study. Changes in left lower lobe blood flow in relation to total cardiac output were studied in response to ventilation of the lobe with normoxic and hypoxic (nitrogen) gas mixtures, with and without the addition of potent inhaled anaesthetic agents [5]. Selective ventilation of the left lower lobe with nitrogen alone (i.e. hypoxia) resulted in a 53% reduction in blood flow to the lobe. Responses to lobar hypoxia were re-measured during the administration of potent inhaled agents at 1 and 2 MAC concentrations, both to the left lower lobe and to the rest of the lung. Isoflurane and fluroxene inhibited lobar HPV by 50% at 2 MAC. Nitrous oxide (0.3 MAC) caused a slight but significant inhibition, while halothane and enflurane caused slight but non-significant changes in lobar HPV. Administration of anaesthetics to the whole lung produced almost identical effects on HPV as when administration was confined to the test lobe alone [42]. It was concluded that nitrous oxide, isoflurane and fluroxene locally inhibit HPV and thereby increase total venous admixture, while halothane and enflurane do not have this effect [5]. Indeed, halothane slightly enhanced HPV in that study. Interestingly, in a subsequent report from the same laboratory and using the same dog model, it was found that HPV was unaffected during both light and deep isoflurane anaesthesia [52]. The authors were unable to explain why their results were at variance with those reported previously [5, 42].

The above results also differed from those obtained using *in vitro* preparations. Possible sources of difference may be related to the methods used to measure HPV. In the *in vitro* studies [10, 15, 40, 59, 63], lungs were perfused at constant flow and the HPV response measured by changes in pressure. In the *in vivo* non-intact models, electromagnetic flowmeters were used to assess changes in blood flow to the hypoxic lobe or lung. Other differences in methods used in the *in vitro* and *in vivo* non-intact preparations include presence (or absence) of perfusion pulsations, perfusion fluid composition, baroreceptor reflexes, absence of bronchial blood flow (which abolishes all central and autonomic nervous activity in the lung), chemical and humoral influences, lymph flow influences and the use of different species [2].

In vivo *intact preparations*

Sykes and his co-workers used an intact dog model to study the effects of nitrous oxide and halothane on HPV [60, 62]. In this model, each lung was ventilated separately but synchronously, one with 100% oxygen and the other with 100% oxygen or a test gas mixture. The HPV response was assessed by measuring the redistribution of blood flow between the two lungs. This was achieved using an infusion of xenon-133 into the inferior vena cava and measuring the mixed expired concentration of xenon emanating from each lung. In these studies the ratio of blood flows between the two lungs was deemed to be equal to the ratio of xenon counts between the two lungs. In one study [62], one lung was ventilated with nitrogen or nitrous oxide while the other was ventilated with 100% oxygen. The results showed that the vasoconstrictor response to nitrous oxide was less than that to nitrogen, and that this difference occurred in the absence of changes in pulmonary arterial pressure, pulmonary capillary wedge pressure or cardiac output. Interestingly, in this study there were no significant differences between Pa_{O_2} values during unilateral hypoxia with nitrogen and those with nitrous oxide, even though blood flow to the hypoxic lung was greater during ventilation with the latter. One possible explanation for this observation was that nitrous oxide caused a decrease in $\dot{V}/\dot{Q}$ ratio in the hypoxic lung, causing less oxygen to be extracted from mixed venous blood during passage through the lung and tending to offset the effects of increased shunt on Pa_{O_2} [62]. Using a similar model, Sykes and colleagues [60] found that there was no significant alteration of the HPV response by halothane in 0.5–1.5% inspired concentrations.

Naeije and colleagues [45] compared halothane, enflurane and isoflurane in intact dogs ventilated (both lungs) in mildly hyperoxic conditions and challenged with short periods (10 min) of hypoxia ($FI_{O_2} = 0.1$). Arterial pressures were monitored via pulmonary arterial and abdominal aortic catheters. The three agents produced similar haemodynamic changes, but only isoflurane inhibited hypoxia-induced increases in pulmonary vascular resistance which were associated with a slight deterioration in arterial oxygenation in both normoxic and hypoxic conditions. This occurred at 0.5, 1.0, and 1.5 MAC isoflurane [45]. In this study, changes in pulmonary vascular resistance index were used as a measure of HPV activity, based upon which only isoflurane inhibited the response. Such studies in intact animals are obviously subject to numerous confounding variables as a result of other changes in the cardiorespiratory systems and errors associated with their measurement.

Overall, the findings of the *in vivo* intact studies are in general agreement with those of the *in vivo* non-intact, but differ from those of the more easily controllable *in vitro* studies. The discrepancies among results are attributable to many factors associated with the type of preparation used. Thus *in vitro* studies utilized denervated lungs, deprived of bronchial and lymphatic circulations, and usually perfused with non-pulsatile flows. Species differences may also be important.

Site of inhibition of HPV by potent inhaled anaesthetic agents

This question has been addressed by Bjertnaes, Hauge and Torgrimsen [14], who used an isolated rat lung preparation. They studied the inhibition of a standardized HPV response during the administration of halothane via the airways, the pulmonary artery by normal anterograde perfusion of the preparation, and the pulmonary veins by retrograde perfusion of the preparation. Halothane inhibited HPV most effectively when administered via the airways, less when presented to the arterial, and least when presented to the venous segments of the pulmonary vasculature. It was therefore concluded that HPV is inhibited by halothane at some extravascular site on the arterial side of the pulmonary vasculature, functionally closer to the alveoli than to the responding vessels [14].

I.v. Anaesthetic Agents

Bjertnaes [10] used an isolated perfused rat lung model (in which profound depression of HPV had been observed with potent inhaled agents) to study the effects of i.v. agents, including fentanyl, pentazocine, ketamine, droperidol, diazepam, thiopentone and pentobarbitone, each of which was administered via the perfusion circuit. In doses which produced clinically useful concentrations in the perfusate solution, none of these agents was recorded to have any effect on HPV.

Because potent inhaled agents had been shown to depress HPV maximally when given via the airways [14], Bjertnaes, Hauge and Kriz [13] also examined the effect on HPV of nebulized fentanyl given via the airways compared with via the perfusion circuit, in the isolated rat lung model. No inhibition of HPV was seen with fentanyl via either route of administration.

In an *in vivo* non-intact preparation (left lower lobe dog lung model) in which nitrous oxide, isoflurane and fluroxene (but not halothane) had been shown to inhibit HPV, no such inhibition was found with the administration of thiopentone, ketamine, pethidine, lignocaine or chlorpromazine [5].

Lumb and colleagues [30] used an intact dog model (*in vivo* intact) to compare shunt fractions ($Qs/Qt\%$) during ketamine infusion with those during halothane anaesthesia. They reported a consistently lower $Qs/Qt\%$ with ketamine, and claimed that no factor other than the anaesthetic agents could account for this difference. They concluded that ketamine resulted in better maintained HPV than did halothane anaesthesia.

Thus, based upon the findings of the *in vitro*, *in vivo* non-intact, and *in vivo* intact animal model studies, it is generally considered that inhaled anaesthetics inhibit HPV, whereas i.v. agents do not [12].

Studies in Humans

Studies in humans are perhaps of greatest significance because the clinical relevance of HPV is of greatest interest to anaesthetists. Such studies, however, are the most difficult to perform and to control for confounding variables.

Perfusion scan studies

Pulmonary perfusion scanning (scintigraphy) has been used to evaluate the effect of inhaled agents on human HPV. Bjertnaes [11] studied two groups of young male volunteers who were scheduled to undergo surgery on the periphery (not abdominal or thoracic). The subjects underwent arterial cannulation for monitoring of arterial blood-gas tensions, Pa_{O_2} in particular. Baseline Pa_{O_2} values were obtained with the patients awake and breathing room air. Under i.v. anaesthesia (thiopentone, fentanyl, pancuronium), unilateral hypoxia was induced in both groups by ventilating the test lung with 100 % nitrogen and the other with 100 % oxygen using a double-lumen bronchial (Carlens) tube.

In each group of subjects the period of unilateral hypoxia was divided into two sequences, one with and one without a potent inhaled anaesthetic (halothane or diethyl ether). In 10 subjects (group A) inhaled anaesthesia was administered during the second sequence, and in seven subjects (group B), inhaled anaesthetics were administered during the first sequence. The distribution of blood flow to the test lung during air breathing and following each of the two sequences of unilateral hypoxia was assessed by lung scintigraphy. Thus one lung was made hypoxic and Pa_{O_2} values were followed until they stabilized, at which time blood flow diversion as a result of HPV was thought to be maximal and sustained. An i.v. injection of isotope-labelled albumin was made so that the macroaggregates would be distributed to and trapped in the lungs, according to the differential pulmonary blood flow. The inhaled agent was then introduced (group A) or withdrawn (group B) and the Pa_{O_2} values followed until another steady state was achieved. At this time, a second injection of macroaggregates, labelled with a different isotope, was made so that subsequent scanning could provide information on pulmonary blood flow distribution at both times of interest. In group A, hypoxia caused the median test lung blood flow distribution to decrease from 49 % of total pulmonary flow (two lungs, $FI_{O_2} = 0.21$) to 25 % (i.v. anaesthesia, unilateral hypoxia). After ipsilateral inhaled anaesthesia was added, blood flow increased to 34 % of total pulmonary flow. This increase was significant for both diethyl ether and halothane subgroups. Blood flow distribution to the test lung during the first period of unilateral hypoxia was significantly greater during diethyl ether or halothane administration (group B) than during i.v. anaesthesia alone (group A). The inhibitory effect of the two inhaled anaesthetics on this response to hypoxia was observed at clinically used blood concentrations of these agents. It was concluded that diethyl ether and halothane inhibit HPV in humans and that this contributes to the development of arterial hypoxaemia during anaesthesia [11]. The scintillation perfusion scans obtained during the various stages of the study appeared to provide fairly convincing evidence that HPV does occur in humans.

One-lung anaesthesia studies

One situation in which HPV would be helpful is in patients undergoing one-lung anaesthesia for thoracic surgery. In this situation the target lung is collapsed (in contrast to being ventilated with nitrogen) and the other lung is ventilated. A number of studies have attempted to draw conclusions about the effects of anaesthetics on HPV from measurements made during one-lung anaesthesia.

Weinreich, Silvay and Lumb [69] used a continuous infusion of ketamine in 110 patients undergoing one-lung anaesthesia. They postulated that, because ketamine has positive effects on the cardiovascular system and is an i.v. agent with no inhibitory effect on HPV, it should produce improved oxygenation. They found that none of their 110 patients had a Pa_{O_2} of less than 9.3 kPa when FI_{O_2} was 1.0, compared with other studies [65, 67] in which halothane was used and 15–25 % of the patients had a Pa_{O_2} less than 9.3 kPa with $FI_{O_2} = 1.0$ [65, 67]. Although the Weinreich study had no control group, the authors suggested that ketamine provides a satisfactory alternative to the potent volatile agents for one-lung anaesthesia [69].

Rees and Gaines [48] compared a ketamine–oxygen technique with an enflurane (1–3 % inspired concentration) technique in 24 patients undergoing one-lung anaesthesia. The Pa_{O_2} and Qs/Qt % values were compared between the two groups of 12 patients studied. No significant differences in Pa_{O_2} or Qs/Qt % were found, but stroke volume index, left ventricular stroke work index and cardiac index were all significantly greater with ketamine. These results suggested that ketamine afforded no advantage, in terms of Pa_{O_2} or Qs/Qt %, over enflurane during one-lung anaesthesia.

Rogers and Benumof [50] theorized that, if inhaled anaesthetics significantly inhibit HPV in humans and all other factors which might influence Pa_{O_2} remain "relatively constant", the administration of inhaled anaesthetics during one-lung ventilation should decrease Pa_{O_2}. They therefore measured Pa_{O_2} before, during and after the administration of halothane or isoflurane to 20 patients undergoing thoracotomy under i.v. anaesthesia and one-lung ventilation. Ten patients received halothane and 10 isoflurane. Within each of those groups, five patients received ketamine and five methohexitone as the i.v. anaesthetic.

The procedure involved five stages:
Stage 1 = Two-lung ventilation, i.v. anaesthesia.
Stage 2 = One-lung ventilation, i.v. anaesthesia.
Stage 3 = Discontinue i.v. agent, start inhaled agent, one-lung ventilation.
Stage 4 = Discontinue inhaled agent, restart i.v. agent, one-lung ventilation.
Stage 5 = Two lung ventilation, i.v. anaesthesia.

The results showed no significant differences in Pa_{O_2} between stages 2 and 3, or between 3 and 4, in both the halothane and isoflurane groups. There was, however, a small (but not statistically significant) decrease in both cardiac index and pulmonary arterial pressure with the administration of the inhaled agent in both the halothane and isoflurane groups. These authors [50] considered that other variables tending to affect Pa_{O_2} had remained "fairly constant" throughout and concluded that the inhaled agents at about 1 MAC do not significantly affect HPV in humans.

Carlsson and colleagues studied HPV in humans whose lungs were exposed to enflurane [20] or isoflurane [18] anaesthesia, comparing the responses with those obtained during i.v. barbiturate anaesthesia. In these studies, patients' lungs were ventilated separately using a double-lumen tube. The test lung was made hypoxic by ventilation with 6–8 % oxygen in nitrogen, while the other lung was ventilated with 100 % oxygen. Cardiac output was determined by thermodilution and distribution of blood flow between the lungs was assessed from the elimination of continuously infused sulphur hexafluoride (SF_6), a poorly soluble inert gas. Application of the hypoxic challenge resulted in decreased blood flow to the test lungs, and the subsequent addition of 2 % enflurane [20] or 1.0–1.5 % isoflurane [18] caused no significant change in the distribution of pulmonary blood flow. When the hypoxic challenge was discontinued, all variables returned to control values. These findings suggested that, in the concentrations used, enflurane and isoflurane have no measurable effect on HPV in humans.

In the isoflurane study [18], however, hypoxic lung blood flow did increase (but not significantly) at an end-tidal isoflurane concentration of 1.5 %. This suggested that isoflurane might have a slight effect on HPV which might perhaps have been better revealed by a more hypoxic challenge (< 8 % oxygen) [18]. In addition, measurements were made after 15-min periods of breathing a new gas mixture. This was considered reasonable because a previous study (from the same group) had concluded that the hypoxic challenge to one lung in an i.v. anaesthetized human subject elicited a maximum vasoconstrictor response within the first 15 min and that this response could not be potentiated by repeated challenges [8]. Furthermore, there was no further potentiation or diminution of the HPV response during a 60-min period of hypoxia [19].

These studies [8, 18–20] used SF_6 elimination as an indicator of differential lung blood flow. This method for separate lung blood flow measurement has been compared with the use of electromagnetic flowmeters and elimination of carbon dioxide in dogs in which one lung was made hypoxic by ventilation with 8 % oxygen or 100 % nitrogen [21]. There was good correlation between flows measured by the probe and by SF_6 methods. Poor results were obtained with the carbon dioxide elimination method, which could be explained by its dependence on the $\dot{V}/\dot{Q}$ ratio and the effect of Pa_{O_2} on the carbon dioxide binding capacity of blood. The carbon dioxide output method could also over-estimate blood flow to an hypoxic lung as a result of the increased alveolar–capillary carbon dioxide gradient [67]. Although the carbon dioxide elimination method has been claimed to be reliable [9], it is considered by the reviewer to be inaccurate and its errors not easily corrected. The use of an inert poorly soluble gas such as SF_6 is considered preferable for measuring differential lung blood flows [21]. From a practical point of view, however, elimination of carbon dioxide is readily measured in most laboratories and clinical settings, whereas relatively few centres have the facilities to measure SF_6 concentrations.

Benumof, Augustine and Gibbons [4] questioned if failure to detect an effect of isoflurane on HPV in humans in two previous studies [18, 50] might have been the result of the relatively short duration of exposure to the inhaled agent, so that clinically relevant tissue concentrations were not achieved. They therefore studied the effect of inhaled anaesthetics on Pa_{O_2} and Qs/Qt % by first establishing a long duration of inhaled anaesthesia ($FI_{O_2} = 1.0$; end-tidal values $\geqslant 1$ MAC for 1 h) with stable one-lung collapse and then, while keeping one lung atelectatic, discontinuing the inhaled agent and introducing i.v. agents (fentanyl, diazepam, thiopentone). In this study, the mean (SD) values for Pa_{O_2} during one-lung ventilation with halothane were much lower than those with isoflurane (15.5 (8.1) *vs* 30.9 (12.9) kPa), which

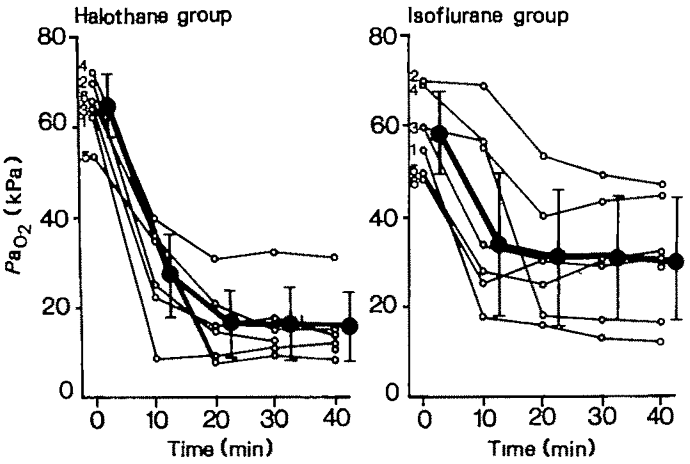

FIG. 2. Serial Pa_{O_2} measurements (mean (SD)) during conversion from two-lung ventilation to one-lung ventilation at time 0 in six individual patients (1–6) in both the halothane and isoflurane groups. The mean Pa_{O_2} value at the end of two-lung ventilation and just before beginning one-lung ventilation is the same as the first mean Pa_{O_2} value in figure 3, and the last (40-min) mean one-lung ventilation Pa_{O_2} value is the same as the second mean Pa_{O_2} value in figure 3. (Adapted from [4] by permission of the author and publisher.)

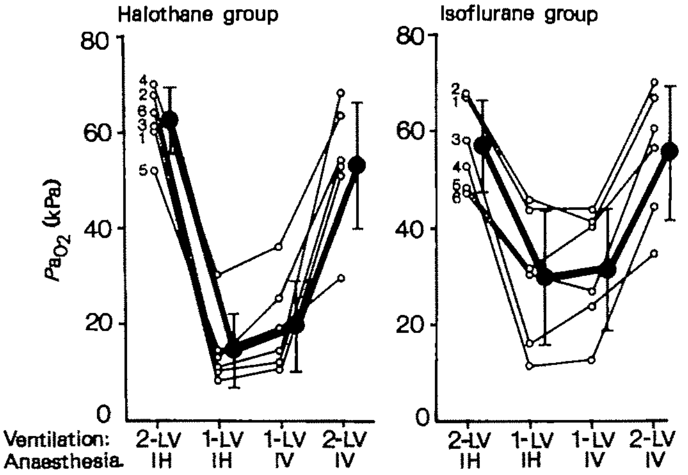

FIG. 3. Pa_{O_2} values during the four experimental sequence steps in individual patients (1–6). Conversion from two-lung ventilation (2-LV) to one-lung ventilation (1-LV) during inhalation anaesthesia (IH) (first two values at left) in both groups caused a very large and significant decrease in Pa_{O_2}. Conversion from IH to i.v. anaesthesia (IV) during 1-LV (middle two values in both groups) caused a slight but significant increase in Pa_{O_2} in the halothane group, and a very slight and non-significant increase in Pa_{O_2} in the isoflurane group. Conversion from 1-LV to 2-LV during IV (last two values at right) caused a very large and significant increase in Pa_{O_2} in both the halothane and isoflurane groups. (Adapted from [4] by permission of the author and publisher.)

was consistent with greater depression of HPV by halothane, compared with isoflurane (fig. 2). Discontinuing halothane and introducing i.v. anaesthesia during one-lung ventilation caused a slight but significant increase in Pa_{O_2} (5.2 (3.9) kPa (fig. 3)) and decrease in Qs/Qt % (7 (2) % (fig. 4)). Discontinuing isoflurane caused a slight but non-significant increase in Pa_{O_2} (1.7 (2.5) kPa) and decrease in Qs/Qt% (2 (2) %). The authors calculated that the atelectatic lung had active HPV and that the slight decrease in shunt and increase in Pa_{O_2} when changing from inhaled to

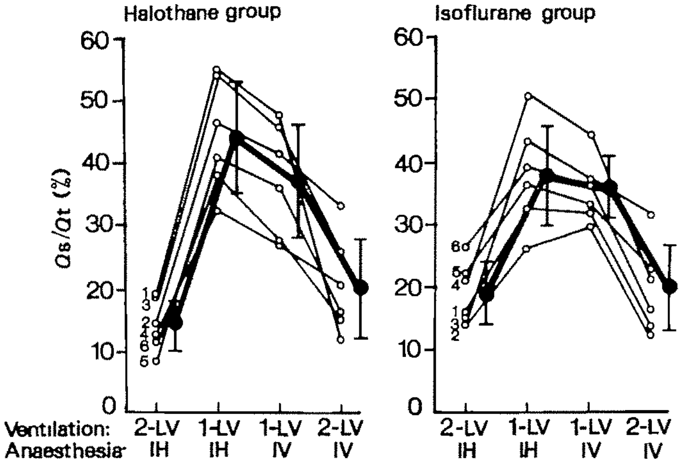

FIG. 4. Shunt (Qs/Qt) values during the four experimental sequence steps in six individual patients (1–6). Conversion from two-lung ventilation (2-LV) to one-lung ventilation (1-LV) during inhalation anaesthesia (IH) (first two values at left) in both groups caused a very large and significant increase in Qs/Qt. Conversion of IH to i.v. anaesthesia (IV) during 1-LV (middle two values) caused a slight but significant decrease in Qs/Qt in the halothane group, and a very slight and non-significant decrease in Qs/Qt in the isoflurane group. Conversion from 1-LV to 2-LV during IV (last two values at right) caused a very large and significant decrease in Qs/Qt in both the halothane and isoflurane groups. (Reproduced from [4] by permission of the author and publisher.)

i.v. anaesthesia was consistent with the findings in animal studies [4]. They further concluded that, because continuous positive airways pressure (CPAP) to the non-dependent lung is usually effective in improving Pa_{O_2} during one-lung anaesthesia, "the use of halogenated drugs in patients undergoing one-lung ventilation is no longer a significant issue" [4].

In subsequent correspondence concerning the above study, Marshall pointed out that the efficacy of CPAP in relieving hypoxaemia "does not mean the problem is solved" [33]. He concluded that the data of Benumof, Augustine and Gibbons [4] showed that hypoxaemia is a frequent cause of concern during one-lung ventilation, and that the choice of anaesthetic agent has a significant effect, halothane being associated with a large probability and greater incidence of hypoxaemia. He also suggested that the variability of the inhibition of HPV is probably different between halothane and isoflurane, being greater with isoflurane, and that, because the Pa_{O_2} increased significantly when halothane was replaced with an i.v. agent, the choice of inhaled *vs* injectable agent may be important [33]. In response to the latter point, Benumof stated that his data did not support that conclusion because the patients who had the lowest Pa_{O_2} during halothane/one-lung ventilation had the smallest increase in Pa_{O_2} when changed to i.v. anaesthesia/one-lung ventilation, while those who had the greatest Pa_{O_2} during halothane/one-lung anaesthesia had the largest increase in Pa_{O_2} when switched to i.v. agent/one-lung anaesthesia [33].

Differences between the results from in vitro *and* in vivo *studies*

In general the differences in results between the *in vitro* (clear inhibition of HPV by inhaled agents) and *in vivo* studies (no inhibition of HPV or difficult to demonstrate) are striking. This prompted the suggestion that other variables may have been obscuring the effects of HPV in the *in vivo* studies [37]. One such variable is cardiac output, which is altered to a markedly different extent by different inhaled agents. Marshall and Marshall [37] collected data from a large number of published studies and plotted the HPV ratio (defined as % flow to the hypoxic segment with anaesthetic/% flow without anaesthetic) as ordinate against cardiac output ratio (defined as cardiac output with anaesthetic/cardiac output without) as abscissa, measured at the same time (fig. 5). The regression line drawn through the points showed:

$$\text{Effect of anaesthetic on HPV ratio} = 0.46+0.83\times(\text{cardiac output ratio})\ (r=0.74).$$

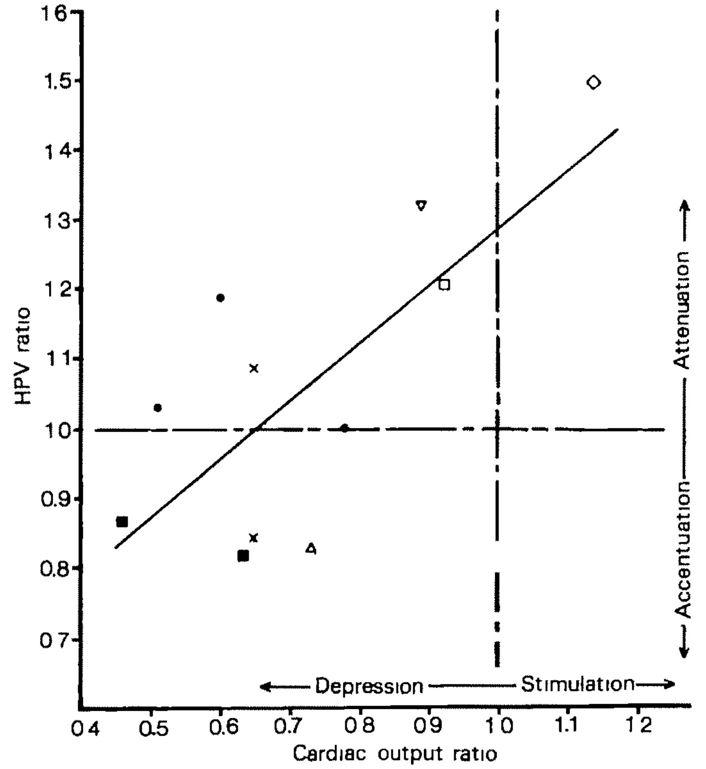

FIG. 5. Effects of inhalation anaesthetics *in vivo*. Observed changes in HPV response with inhalation anaesthetics are compared with simultaneous changes in cardiac output; data have been standardized to allow comparison between studies. Cardiac output ratio = cardiac output with anaesthetic/cardiac output without anaesthetic. Control cardiac output in absence of inhalation agents is designated 1.0. The HPV response (HPV ratio) is indicated by comparing hypoxic segment flow with and without inhalation anaesthesia. If the anaesthetic has no effect, the value is 1.0; if the response to HPV is reduced, the value is > 1.0, and if response to HPV is enhanced, the value is < 1.0. Significant linear relationship of various studies is shown: anaesthetic action on HPV ratio = 0.46 + 0.83(cardiac output ratio); $r = 0.74$. These results suggest that changes in cardiac output in the presence of inhalation agents are an important influence on whether the response to HPV will appear to be increased or decreased. ● = Halothane [42, 60, 61]; ■ = isoflurane [52, 60]; △ = methoxyflurane [32]; □ = nitrous oxide [62]; ▽ = trichloroethylene [58]; ◇ = diethyl ether [61]; x = enflurane [42]. (Reproduced from [37] by permission of the American Physiological Society and the author.)

This relationship reveals that, in the presence of inhaled anaesthetics, the efficacy of HPV varies inversely with cardiac output. During inhalation anaesthesia, a direct inhibition of HPV may be offset by an enhanced responsiveness as a result of decreased cardiac output, with the result that flow diversion and gas exchange (as assessed by Pa_{O_2}) and, by inference, HPV may all appear to be unaffected (fig. 6).

Domino and colleagues [25] studied the influence of locally administered isoflurane on the regional HPV response over a range of cardiac outputs in closed-chest dogs. In this preparation the right lung was ventilated with either 100% oxygen or a hypoxic mixture. Various alveolar concentrations (0.0, 1.0 and 2.5 MAC) of isoflurane were administered to the left lung. Cardiac output was varied by opening and closing surgically created arteriovenous fistulae and the HPV response was measured by differential elimination of carbon dioxide, and by venous admixture. In this model, when the effects of different concentrations of isoflurane on Qs/Qt % during left lung hypoxia were studied under stable conditions of cardiac output, mixed venous and alveolar oxygen tensions, and pulmonary arterial and wedge

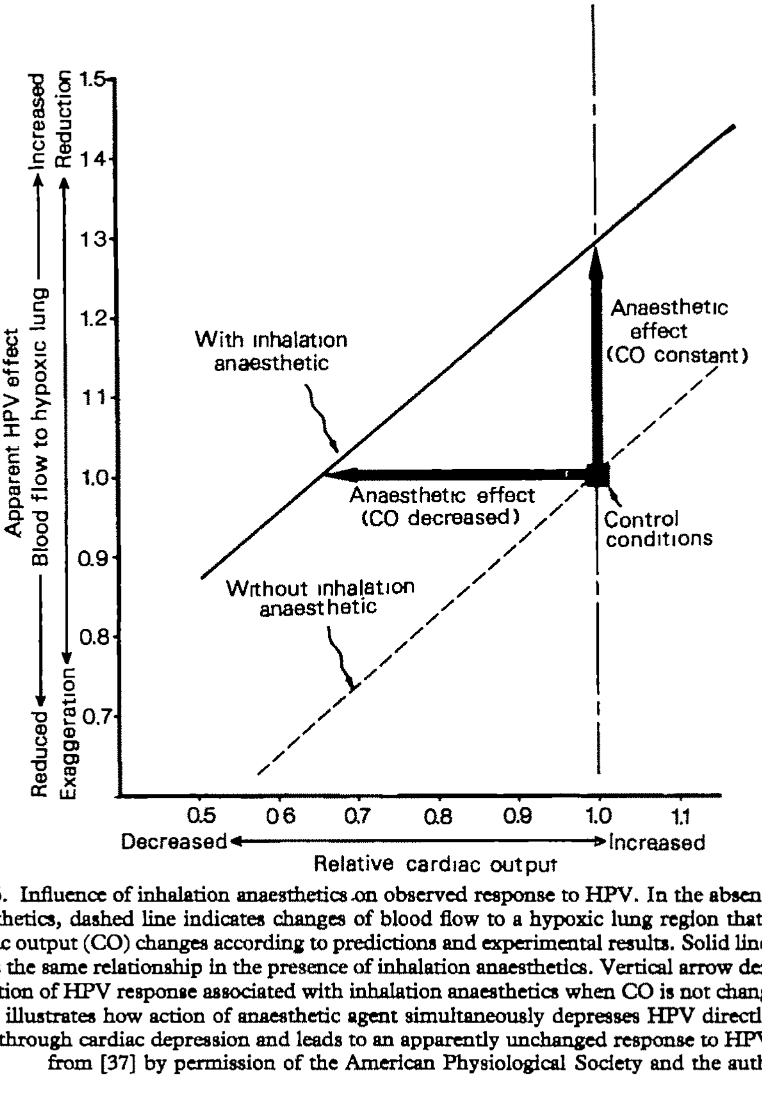

FIG. 6. Influence of inhalation anaesthetics on observed response to HPV. In the absence of inhalation anaesthetics, dashed line indicates changes of blood flow to a hypoxic lung region that occurs as total cardiac output (CO) changes according to predictions and experimental results. Solid line parallel to this shows the same relationship in the presence of inhalation anaesthetics. Vertical arrow demonstrates true reduction of HPV response associated with inhalation anaesthetics when CO is not changed. Horizontal arrow illustrates how action of anaesthetic agent simultaneously depresses HPV directly and enhances HPV through cardiac depression and leads to an apparently unchanged response to HPV. (Reproduced from [37] by permission of the American Physiological Society and the author.)

pressures, the results revealed a significant direct effect of the dose of isoflurane:

$$\% \text{ depression of HPV} = [(22.8 \times \% \text{ alveolar isoflurane}) - 5.3]$$

with an ED$_{50}$ of 2.4% isoflurane (alveolar concentration) for the response. These authors also demonstrated that, during left lung hypoxia, increasing the cardiac output caused an increase in both left lung blood flow and venous admixture. Thus, when many of the variables were kept constant, an inhibitory effect of isoflurane on HPV could be demonstrated in this *in vivo* intact model [25]. The interpretation of that study and its clinical implications were discussed elegantly by Benumof in an accompanying editorial [3].

The HPV–cardiac output relationship provides a plausible explanation for some of the discrepancies in results between the *in vivo* and *in vitro* studies and for the apparent lack of differences between the effects of i.v. and inhaled agents during one-lung anaesthesia in many of the human studies. Indeed, an increase in cardiac output, as may occur with some of the i.v. agents, might even be construed as being detrimental to the normal HPV response, and it could be argued that these agents should be avoided because of their indirect inhibitory effects on HPV. Clearly, many physiological variables must be considered when interpreting the effects of inhaled and i.v. anaesthetics on the pulmonary circulation, and on HPV in particular.

Potentiators of HPV

While much of the previous research has addressed inhibition of HPV and its implications for clinical anaesthesia, more recent studies have investigated potentiators of this response.

Almitrine bimesylate, a respiratory stimulant, was found to improve Pa_{O_2} in patients with chronic obstructive pulmonary disease, even in the absence of ventilatory stimulation [56, 64]. It has been shown to potentiate HPV in intact pentobarbitone-anaesthetized dogs [51], although another study in thoracotomized dogs failed to demonstrate such potentiation [22]. A study using high dose almitrine in a closed-chest unilateral hypoxic lung dog model (similar to that used by Domino and colleagues [25]) found that the drug caused non-specific pulmonary vasoconstriction which was maximal in those vessels having the least initial tone. Constriction was greatest in the lung ventilated with 100% oxygen, compared with the hypoxic lung. Blood flow was therefore diverted from the hyperoxic to the hypoxic lung, diminishing the efficacy of HPV in that lung. Hypoxic lung showed no further increase in vasoconstriction with almitrine and HPV was not enhanced in the hypoxic lung [23].

Hypoxic pulmonary vasoconstriction is reduced by prostacyclin (PGI_2, a potent vasodilator) and potentiated by leukotrienes [44]. Marshall, Kim and Marshall [39] used an isolated rat lung preparation to study the effects of halothane, ibuprofen (a cyclo-oxygenase inhibitor) and BW 755C (a lipoxygenase inhibitor) on the HPV response. They found that HPV was reduced by halothane (as shown previously); that inhibition of cyclo-oxygenase by ibuprofen potentiated HPV; and that when ibuprofen was present the attenuation of the HPV response by halothane was diminished. They also concluded that the products of the lipoxygenase pathway (leukotriene peptide) are essential for HPV, but this conclusion was not shared by Gottlieb and colleagues [27], who studied isolated ferret lungs. Species differences may therefore be of importance when considering the mechanism of HPV.

Lejeune and colleagues [29] studied the effects of 70% nitrous oxide on mean pulmonary arterial pressure (MPAP) – cardiac index relationships in 13 pentobarbitone-anaesthetized dogs with lungs ventilated alternately at FI_{O_2} 0.3 or 0.1. Over a range of cardiac indices, hypoxia increased MPAP in seven "responder" dogs but did not affect MPAP in six "non-responder" dogs. In the latter group, HPV was restored by the administration of a cyclo-oxygenase inhibitor (acetylsalicylic acid 1 g i.v.). In responders, nitrous oxide partially inhibited HPV, while in non-responders with an HPV response restored by acetylsalicylic acid, nitrous oxide did not affect HPV. These findings suggest that the effects of nitrous oxide on the pulmonary vasculature depend upon pre-existing vascular tone and can be modulated by cyclo-oxygenase products of arachidonic acid metabolism. Inhalation anaesthetic agents stimulate release of arachidonic acid from cell membranes [57]. In the non-responder dogs treated with acetylsalicylic acid, increase in HPV by nitrous oxide can be explained by increased formation of vasoconstrictor leukotrienes from the increased amounts of precursor made available. If cyclo-oxygenase inhibitors will have any application for improving oxygenation during clinical anaesthesia has not yet been determined.

Scherer and colleagues [54] infused prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) into the pulmonary artery of an atelectatic lung of anaesthetized paralysed dogs and found that arterial and mixed venous oxygen tensions and calculated venous admixture during stable one-lung atelectasis could be improved. The proposed mechanism was an increase in HPV in the atelectatic lung. In a subsequent study, Scherer, Vigfusson and Lawin [55] found that, in terms of reducing venous admixture and improving arterial oxygenation during one-lung ventilation in dogs, both inflation of the balloon on a pulmonary arterial catheter lying in the artery supplying the atelectatic lung, and infusion of $PGF_{2\alpha}$ were equally effective. In both studies [54, 55] the dogs were anaesthetized with piritramide, an i.v. agent.

Chen and colleagues [24] studied the effect of i.v. $PGF_{2\alpha}$, administered as a continuous peripheral infusion, on the HPV response in a closed-chest dog model during left lung hypoxia. They found that $PGF_{2\alpha}$ caused vasoconstriction in both the right lung receiving 100% oxygen and the left receiving a hypoxic gas mixture, without significantly changing blood flow to either lung. Thus HPV was not enhanced by this non-specific increase in vasoconstriction. The authors concluded that, if PGF$_{2\alpha}$ is to be used to enhance oxygenation during one-lung anaesthesia, the infusion should be confined to the atelectatic lung, as in Scherer's studies. The efficacy of PGF$_{2\alpha}$ during the administration of potent inhaled anaesthetic agents has not yet been reported.

Bindslev, Cannon and Sykes [6] found that lignocaine restored normal HPV in a constant-flow, perfused left lower lobe dog lung preparation (*in vivo*, non-intact). Thus when the left lower lobe was ventilated with 100% oxygen or 7% oxygen in nitrogen, lignocaine had no effect on lobar PVR. Ventilation of the lobe with 7% oxygen in nitrous oxide decreased the response to hypoxia, while the addition of lignocaine restored lobar vascular resistance to a mean value similar to that observed during ventilation with 7% oxygen in nitrogen. Failure of lignocaine to increase lobar vascular resistance during ventilation with 100% oxygen, or 7% oxygen in nitrogen suggests that lignocaine acts directly at the site of HPV inhibition by nitrous oxide, and therefore at the site of alveolar hypoxia.

In a subsequent study [7] the same group found that lignocaine had no effect on lobar blood flow during lobar collapse (atelectasis) whether the right lung was ventilated with 50% oxygen in nitrogen or with 50% oxygen in nitrous oxide. Thus lignocaine reversed the depression of HPV produced by lobar *ventilation* with nitrous oxide. Failure to exert an effect on lobar vascular resistance during atelectasis was thought to be the result of absence of nitrous oxide-induced inhibition of HPV in the atelectatic lobe [7]. The effects of lignocaine on HPV which has been depressed by potent inhaled agents remain to be determined, as do the clinical implications of these observations.

CONCLUSIONS

The effects of anaesthetic agents on the pulmonary circulation and on HPV in particular have been reviewed. Numerous models have been designed to study these effects and the results have not always been consistent, differences in methodology and difficulties in controlling confounding variables being the most likely reasons. In general, HPV is not directly inhibited by i.v. anaesthetic agents, but is directly inhibited by inhalation agents. Because of compensatory mechanisms that may be difficult to measure accurately (particularly in human subjects) the inhibition is usually, but not always, of little clinical consequence. Present consensus is that potent inhaled anaesthetic agents are not contraindicated for thoracic surgery requiring one-lung ventilation when active HPV is most desirable. Indeed, their use has been advocated because of their salutory effect on bronchomotor tone, high potency (allowing high inspired concentrations of oxygen) and rapid elimination [2]. There may, however, be some patients (particularly those with generalized lung abnormalities) in whom hypoxaemia may occur and in these subjects change to an i.v. agent should be considered [4, 33].

Potentiators of HPV remain at the experimental stage and have yet to be investigated in humans. As more is learned about the biochemical basis of HPV, potentiators may eventually offer real benefits to patients who develop hypoxaemia during general anaesthesia.

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PHARMACOKINETIC AND METABOLIC PROPERTIES OF LUNG

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The major purpose of the circulation of the blood through the pulmonary vessels is undoubtedly to effect gas exchange. This seems to have been recognized in the 13th Century by one of the leading physicians in Cairo, Ibn-an-Nafis, who wrote "the blood...must pass along the pulmonary artery to the lungs to spread itself out there and mix with the air until the last drop be purified" (see [50]). Some four centuries later, Boyle restated this purpose: "the Ventilation of Blood in its passage thorow the Lungs; in which passage it is disburthened of Excrementitious Steams" [26] and Richard Lower added, "the blood takes in air in its course through the lungs and owes its bright colour entirely to the admixture of air" [88]. We now also know that, to achieve this exchange, the blood is spread out in a very thin film over the pulmonary capillary surface and is separated from air by a structure consisting of a thin alveolar epithelium, some basement membrane and another thin, vascular endothelium. The pulmonary vascular endothelium is continuous and offers a total surface area of about 70 m^2. Thus the structure maximizing gas exchange between blood and air also maximizes contact between the blood and the largest endothelial cell surface in the body.

It is this extensive endothelial contact that we now recognize as being the basis of one of the major non-respiratory functions of the lung—the ability to metabolize blood-borne substrates on their passage through the pulmonary circulation. This ability has been called the metabolic function, or the pharmacokinetic function, of lung [16], because it deals with what the lung does to the substrate rather than with the responses of the lung to substrate. Most of the substrates investigated are endogenous substances, with less attention paid to exogenous, xenobiotic, drug substrates, but it is already clear that pulmonary pharmacokinetics of drugs are quite different from those of endogenous substrates [21].

The first report of a metabolic transformation of an endogenous substrate in the pulmonary circulation was published in 1925 as the inactivation of a "serum vasoconstrictor substance" in the lung [129]. This substance, later identified as 5-hydroxytryptamine (5-HT), made impossible the perfusion of isolated kidneys with blood but, if the lungs were included in the circuit, such perfusion was feasible for several hours. It is salutary to note that, 55 years later, the same problems were reported with an isolated blood-perfused preparation of dog stomach, which were solved by the same manoeuvre [110]. Inactivation of the now characterized 5-HT on passage through the pulmonary circulation was first shown by Gaddum and colleagues [55] and has been confirmed on numerous occasions in a variety of preparations [16, 62].

The major contribution to the modern development of this research area was that of Vane and his collaborators in the late 1960s. In a series of papers, metabolic activity towards a variety of substrates—biogenic amines, peptides and prostaglandins—was clearly demonstrated in the pulmonary circulation of animals *in vivo*, establishing the extent and specificity of this non-respiratory function [139]. Extension of this solid foundation by several groups of workers has been documented in a number of reviews [16, 58, 62, 81]. The results of this work are summarized in table I, which shows the metabolic properties of lung towards blood-borne substrates, perfused through the pulmonary circulation in normal lungs. It includes exogenous xenobiotic drug substrates,

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TABLE I. *Effect of passage through the pulmonary circulation on biological activity (results from the work of many authors, discussed in greater detail in previous reviews [14, 16, 21, 58, 62, 82])*

Substrate	Consequence of pulmonary transit		
	Activation	Inactivation	No change
Biogenic amines		5-HT Noradrenaline Phenylethylamine	Dopamine Adrenaline Tyramine Histamine
Peptides	Angiotensin I	Bradykinin Enkephalin Atrial natriuretic peptide	Angiotensin II Oxytocin Vasopressin
Eicosanoids	Arachidonic acid	Prostaglandins D_2, E_2 and $F_{2\alpha}$	Prostacyclin (PGI_2)
Adenine derivatives		ATP, ADP, AMP Adenosine	
Steroids	Cortisone	Progesterone Beclamethasone	
Basic drugs		Fentanyl Imipramine Chlorpromazine Lignocaine Propranolol	Morphine Isoprenaline

although these will be discussed separately from the endogenous substrates later in this review.

CHARACTERISTICS OF METABOLIC FUNCTION OF LUNG

For the endogenous substrates, some general features of their metabolic fate in the pulmonary circulation are crucial to the understanding of this pulmonary function. First, the pharmacokinetic function is *metabolic*—that is, a biochemical transformation is the basis of the pharmacokinetic effect and these transformations occur in conscious human subjects and within the physiological range of concentrations [60, 128]. If excessively great concentrations are used, selectivity of metabolism may be lost and sites and modes of metabolism disclosed, which are not relevant to physiological concentrations of substrate.

Two other features arise from the structure of the lungs. First, the entire cardiac output passes through the pulmonary circulation and blood from the lungs passes very rapidly to the periphery. Thus these metabolic operations are performed on the whole of the blood volume and the products are distributed almost immediately to the periphery, where their effects are mediated. Hence the lung can control the pharmacodynamic effects of vasoactive hormones by changes in their metabolic fate in the pulmonary circulation. Second, the respiratory function of the lungs brings the external environment (in terms of inspired air) into continuous and close contact with the cells of the alveolar capillaries and provides a means whereby external factors may alter internal biochemistry, with pharmacodynamic consequences.

The selectivity of the pharmacokinetic process leads to the three results shown in table I: activation, inactivation or no change. The process of activation entails the metabolic *product* being more biologically effective than the *substrate* entering the pulmonary circulation and is best exemplified by the conversion of the inactive decapeptide, angiotensin I (AI), to the highly potent octapeptide, AII. A more frequently observed fate is inactivation and is most clearly seen with 5-HT and with prostaglandin (PG) E_2 (PGE_2) and $PGF_{2\alpha}$, all of which suffer > 90% inactivation on a single transit of the pulmonary circulation. However, the third category in this table—no change—is conceptually the most important because it demonstrates the selectivity of these metabolic functions in lung. For instance, the liver will inactivate PG and 5-HT entering via the portal circulation, but it will not differentiate, as does the lung, between PGE_2 and PGI_2 [14], or between noradrenaline, adrenaline and dopamine [146]. This selectivity of the lung's metabolic functions led Vane [139] to propose the idea of local and circulating hormones, the former, such as bradykinin, 5-HT and PGE_2, being largely inactivated in the pulmonary circulation and, thus, not able to reach the systemic arterial beds and the latter, such as histamine, adrenaline and vasopressin, passing freely through the pulmonary circulation and able to circulate to the periphery.

Sites of metabolism

The lung is said to comprise 40 different types of cell. However, as far as metabolism is concerned, endothelial cells are the most important. For many years, these cells were not considered to be metabolically interesting or even particularly active, but they are now known to exhibit a number of metabolic properties relevant to vasomotor control [109, 123]. Endothelial cells cultured from a variety of sources (aorta, pulmonary artery, umbilical vein, *etc.*) can carry out most of the metabolic reactions associated with the pulmonary circulation, such as conversion of AI to AII, inactivation of bradykinin, enkephalin and 5-HT, and synthesis of PGI_2 [123]. However, there are differences between endothelial cells from different vascular beds and from different levels in the same vascular bed (arterial, microvascular and venous) [57], which could explain discrepancies between results from cultured cells and the vasculature *in situ*. For instance, cultured endothelium, from the pulmonary artery or other sources, will not inactivate PGE_2 [14], whereas there is extensive inactivation in the pulmonary circulation *in situ* [14, 53]. Furthermore, the processes of cell culture themselves can also modify the biochemistry of endothelial cells [1, 57]. Nevertheless, the metabolic functions of lung are frequently taken as expressions of the activities of the pulmonary endothelium.

Mechanisms of selective metabolism

Some of the selectivity of the metabolic functions of lung may derive from the properties peculiar to the alveolar capillary endothelium, but there are at least two other more clearly defined mechanisms of selectivity which depend on the subcellular localization of the metabolic system involved.

First, some of the enzymes concerned are located on the outside of the endothelial cell membrane (ecto-enzymes), with free access to substrates in the extracellular or vascular space. For angiotensin converting enzyme (ACE) this location is more specific, with immunoreactive enzyme being found only on the luminal surface of the endothelium *in situ* [123]. The ecto-nucleotidases (AMPase, ADPase and ATPase) may not be so restricted. For all these ecto-enzymes, the selectivity of metabolism must reflect the selectivity of the enzyme itself. This is certainly true of ACE, which will not hydrolyse peptides without a free carboxy terminal [6]—thus C-terminal amides such as oxytocin and vasopressin pass freely through the pulmonary circulation [16]. The free passage of AII also reflects the substrate specificity of ACE, which will not hydrolyse certain peptide links involving proline [6]. This characteristic has been utilized in the structure of both natural and synthetic ACE-inhibitors [5, 38, 104]. Recently a different, non-enzymic type of peptide inactivation has been shown in lung for the atrial natriuretic peptide (ANP). Labelled ANP was rapidly removed on a single transit through rabbit lungs, but it could then be recovered by displacement with non-labelled peptide [137]. This unusual mode of inactivation is probably attributable to the presence of "silent" receptors (binding sites which do not lead to effects) for ANP in lung [101]. As yet, this is the only example of avid *pharmacokinetic* binding for endogenous peptides in lung.

The other relevant enzymes are within the cell and are consequently separated from their substrates in the blood by the cell membrane. The metabolism of these substrates (5-HT, noradrenaline, PGE_2, adenosine) comprises two distinct processes: uptake across the cell membrane and, subsequently, interaction with the intracellular enzyme. For catecholamines, the uptake process is rate limiting and is the source of the observed specificity [16, 62, 82]. Pulmonary monoamine oxidase will metabolize noradrenaline, dopamine and adrenaline equally well *in vitro*, with a K_m in the range 300–400 μmol litre^{-1} [17] whereas, in whole lung, only noradrenaline is metabolized with a K_m of about 1 μmol litre^{-1} [62]. Uptake is not rate limiting with PGE_2 or $PGF_{2\alpha}$, but the PG uptake system will not accept PGI_2 as a substrate, although the intracellular enzyme prostaglandin dehydrogenase (PGDH) hydrolyses PGI_2 faster than PGE_2 *in vitro* [14]. Here, again, it is the specificity of the uptake system that determines the selectivity of the metabolic process. This discrepancy between the enzymic content and the functions expressed in the organized tissue is frequently observed in lung and is also important in the pharmacokinetics of exogenous, xenobiotic drugs.

The lung as an endocrine organ

Apart from its pharmacokinetic modulation of circulating endogenous substrates, the lung also has the potential for a pseudo-endocrine function [20], by virtue of its central position in the circulation. The release of von Willebrand Factor and tissue plasminogen activator from pulmonary endothelium into the blood perfusing the lung could be considered an endocrine function [109]. The endocrine function will also reflect the overflow into the pulmonary circulation of a mediator formed by lung tissue for intra-pulmonary purposes. Such overflow is more likely in pathological situations. For instance, the release of eicosanoids and histamine from lung during immunological challenge [14], and of eicosanoids in acute injury states (endotoxin, embolism) [29, 79, 92], into the systemic circulation, could add to the general cardiovascular derangements in these conditions.

There are some newer candidates for "pulmonary vasoactive hormone" status. In the past few years, the endothelium has been identified as the source of three more vasoactive mediators: platelet activating factor (PAF), endothelium-derived relaxing factor (EDRF) and endothelin. The phospholipid, PAF, has a wide spectrum of mostly pro-inflammatory activities [27, 91], but is unrelated to the lipid mediators derived from arachidonic acid, although its synthesis is also inhibited by steroids. The most important sources of PAF are leucocytes and platelets, but cultured endothelial cells will release PAF on stimulation with a number of inflammatory mediators [27]. It is not easy to differentiate between endothelium-derived PAF and that from other cells in whole lung, and consequently the contribution of endothelium to the effects of PAF generation in lung is difficult to assess.

The vasodilator substance EDRF [54, 67, 140] has now been identified as nitric oxide [105]. This is formed by endothelial cells in culture or *in situ* by a number of stimuli such as histamine, bradykinin, ATP and acetylcholine. Although its vasodilator action *in vivo* depends on its diffusion abluminally to the underlying smooth muscle, nitric oxide can also be secreted into the lumen and affect platelets (it also has potent anti-platelet-aggregatory activity [3, 75]) or be transferred downstream in the blood. Using blood-free perfusion media, nitric oxide can be "exported" from segments of coronary artery [67] and from perfused hearts [2, 84]. However there have been no reports of a similar export of nitric oxide or of EDRF activity from the large mass of endothelial cells in the pulmonary circulation, although isolated strips of pulmonary artery [34, 47] and isolated lungs [37] show signs of EDRF generation.

There are at least two reasons why the export of EDRF/nitric oxide from lung may be unlikely *in vivo*. Both substances are rapidly oxidized by a variety of oxidizing agents, by the superoxide anion O_2^- and by atmospheric oxygen [105]. The high concentration of oxygen in the lung and pulmonary blood may inactivate more of the nitric oxide formed than in peripheral vascular beds. Furthermore, haemoglobin is a potent inactivator of nitric oxide [105] and the amount of free haemoglobin normally present in blood would be enough to prevent nitric oxide being a circulating hormone. Thus although, in peripheral beds and perhaps even in the bronchial circulation, EDRF/nitric oxide could be an important determinant of vascular function, its significance in the pulmonary circulation remains to be established. One possibility is that hypoxic vasoconstriction could reflect a lack of vasodilator nitric oxide, but this seems to be unlikely in the light of recent results showing the potentiation of hypoxic vasoconstriction by inhibitors of the effects of EDRF [28, 93]. Of particular interest are the reports of the alteration of endothelium-dependent relaxation in vascular smooth muscle strips by halothane, enflurane and isoflurane [23, 97, 130], but the relevance of these results to responses *in vivo* is uncertain.

The third, most recently described endothelial cell product is a 21-amino acid peptide, endothelin. This peptide is a potent vasoconstrictor [145] and bronchoconstrictor [138], released from cultured endothelium by other vasoconstrictors (noradrenaline, AII) or by hypoxia or thrombin. Its release from strips of vascular tissue or perfused vascular beds has not yet been described, although it has been detected, by radioimmunoassay, in human plasma after myocardial infarction [95]. However, passage through the pulmonary circulation of isolated blood-free lungs reduced the activity of endothelin by about 50%, although other vasodilators such as PGI_2 and EDRF were released by endothelin from lung [46]. The pulmonary circulation has the potential to generate endothelin from its own endothelium, given an appropriate stimulus such as hypoxia, which is known to release vasoconstrictors from endothelium [121] or perhaps isoflurane, an endothelium-dependent contractor of rat aorta [130].

One of the major problems in this area is to make physiological sense out of the conflicting activities of the endothelial cell products, both for the underlying smooth muscle and for the blood cells in the lumen. Some part of an answer may involve a selective output by endothelial cells in different vascular beds, as already seems likely for PG synthesis [57].

In summary, under normal conditions, the pulmonary circulation provides a selective metabolic control *in vivo* over endogenous substrates in pulmonary arterial blood by virtue of the close contact with pulmonary endothelium endowed with selective metabolic processes. This control system can be disturbed by a number of factors, which will be discussed below.

PHYSIOLOGICAL FACTORS

If the metabolic functions of the lung are of physiological significance, then they should be susceptible to modulation by extrapulmonary, physiological factors.

Age and hormones

Age-related structural changes in lung are particularly obvious around birth: the rapid increase in alveolar capillaries, following birth, is accompanied by the expected increases in ACE activity [114]. Perinatal changes in PGE_2 metabolism, PG synthesis and monoamine oxidase (MAO) activities in lung have also been reported [14, 19]. The physiological significance of these changes has not yet been established; nevertheless, it seems that the pharmacokinetic function of lung towards endogenous substrates—like the pharmacokinetic capability towards drugs—is deficient in neonates and takes time to develop fully. By analogy with other metabolic functions, advanced age would also decrease those of the lung and evidence of this has been shown with propranolol in rat lung [77].

Although the lung is not usually considered a target organ for sex hormones, it contains receptors for oestrogens, androgens and prolactin [20]. Furthermore, pulmonary metabolism of 5-HT, phenylethylamine, arachidonate and PGE_2, in rats, was affected by the oestrous cycle [10, 11, 14]. This susceptibility to physiological changes in concentrations of endogenous steroids suggests that pulmonary pharmacokinetics could also be altered by pharmacological changes in steroids, for instance with oral contraceptives. Hormonal deficiency, as represented by diabetes induced by streptozotocin, decreased ADP hydrolysis and PGI_2 synthesis in rat lung [12, 143], both changes decreasing the anti-platelet-aggregatory potential of the pulmonary vessels, although 5-HT clearance in this model was not affected [141]. These changes are compatible with those in the systemic circulation in diabetic subjects in whom increased platelet aggregation and vascular pathology are seen.

Species

Species differences in many physiological functions are common and these differences are important in so far as animal tissues are used as models or analogues of human tissues. For instance, the metabolism of arachidonic acid via the cyclo-oxygenase pathway has, as its major products, PGI_2 and thromboxane (TxA_2)—two potent agents with opposing biological activities. In guineapig lung, the balance is in favour of TxA_2 but, in lungs from many other species including rats and man, the balance is in favour of PGI_2 [14, 51], even during as potent a pathological stimulus as immunological challenge [125]. The inference from this must be that guineapig lung is not a good model of human lung when arachidonate metabolism is being studied.

However, with a different substrate, ADP, a different conclusion is reached. In rat and hamster lungs, ADP was rapidly hydrolysed to AMP, and AMP itself was relatively resistant to further breakdown whereas, in guineapig and human lung, ADP was broken down to adenosine with very little AMP surviving [36]. Since adenosine is a potent anti-aggregatory substance, this species difference could be important in models of the anti-aggregatory mechanisms exhibited by the pulmonary circulation and possible mechanisms for their alteration.

The susceptibility of each possible substrate to each possible physiological variation has not yet been assessed, but enough has been done to show that the metabolic functions of the pulmonary circulation are indeed responsive to modulation by physiological, extrapulmonary factors. The nature of this response will vary from substrate to substrate, as would be expected from a physiological mechanism.

PHARMACOLOGICAL AND PATHOLOGICAL FACTORS

Drug effects

The simplest pharmacological factors affecting the metabolism of endogenous substrates are drugs known to interfere with the enzymes or uptake systems involved. The metabolism of the monoamines, 5-HT and noradrenaline, was decreased by blockers of neuronal Uptake$_1$ and by inhibitors of MAO [16, 17, 62, 82] in concentrations equivalent to those used to alter neuronal function in the CNS. Thus it is very likely that patients treated with tricyclic antidepressants or MAO-inhibitors for disorders of affect or mood will also have a decreased monoamine metabolism in their lungs.

The ACE inhibitors now used widely in cardiovascular medicine were originally developed from work on the properties of lung ACE [4, 104]. Although the ACE on *all* cells will be inhibited, the effects on the lung enzyme must be a significant part of the overall action of these drugs. Inhibition of bradykinin inactivation (another consequence of ACE inhibition) is unlikely to contribute to the therapeutic effects of ACE inhibition, as there are other highly active bradykininases in plasma and tissues [7] to substitute for ACE as a means of inactivating bradykinin.

Prostanoid synthesis in lung is as susceptible as in other tissues to inhibition by indomethacin and its congeners [14]. Clearance of PGE$_2$ and PGF$_{2\alpha}$ in the pulmonary circulation can be blocked effectively by a variety of drugs [14], but for most of them this activity is not relevant to their clinical effects. However, inhibition of PG clearance by indicator dyes (indocyanine green [8, 112]) and sulphasalazine [76] could contribute significantly *in vivo*.

Anaesthetic agents are a particularly important group of drugs in terms of their potential to interfere with the metabolic function of the lung. I.v. agents have not been studied, but local anaesthetics such as bupivacaine [120] did not affect 5-HT uptake in rabbit isolated lung. The inhalation agents have received more attention in a variety of models. In the simplest, isolated lungs of rat or rabbit were perfused with saline solution equilibrated with the agent being investigated [39, 100]. In these lungs, 50% (v/v) nitrous oxide in oxygen, 0.5–2% halothane or enflurane and 1–4 MAC isoflurane all depressed noradrenaline, 5-HT and phenylethylamine metabolism. In other models, halothane and other halogenated hydrocarbons were delivered only in the ventilating gas [73] or both by ventilation and in the perfusate [142]. Halothane inhibited noradrenaline inactivation *in vivo* in dogs, but not the metabolism of PGE$_2$ [14]. These results can be interpreted as showing a disruption, by the anaesthetic agent, of the cell membrane structures needed for uptake of the amines and so preventing their access to the intracellular metabolizing enzyme, MAO.

Surprisingly, in view of the unanimity of the results from animals, clinical studies showed no difference in pulmonary removal of 5-HT in patients before, during and after general anaesthesia [43, 60]. It is possible that this discrepancy reflects the concentrations of halothane used as, in the experimental studies, the inhibition was dose-related. However, interactions between inhalation anaesthetics and endogenous monoamines would be important pharmacological considerations in the practice of anaesthesia and more clinical studies are needed to confirm or refute this possibility.

A more common, more complex and more toxic "drug" is tobacco smoke. The epithelial cells are probably the most involved in the link between lung cancer and the carcinogens in tobacco smoke and it is tempting to suggest that some modification of *endothelial* function by components of tobacco smoke is involved in the *cardiovascular* sequelae of smoking. Several experimental studies have been made of the acute effects of cigarette smoke as a component of the ventilating gases, and of the chronic effects after days of exposure. In rat and hamster isolated lungs, ventilation with cigarette smoke decreased metabolism of 5-HT [83] and PGE$_2$, in proportion to the tar content of the cigarette [14]. This is presumably an acute effect, as lungs from rats, exposed to smoke for up to 10 days but not ventilated acutely with smoke, did not show such changes [14]. Metabolism of arachidonate to prostanoids or to lipid was also affected by smoke ventilation of isolated lungs [14]. In man, an acute effect of cigarette smoking was a decrease in production of PGI$_2$ in smokers but not in non-smokers [99].

Pathological factors

A major problem in the analysis of abnormal metabolism lies in deciding whether it results from changes in quantity or in quality. In the pulmonary circulation, this can be translated into *haemodynamic* changes—that is, in flow rate, transit time and surface area available—and *biochemical* changes where the metabolic capacities of the cells have changed. The biochemical analysis using Michelis–Menten kinetics also presents problems, as most of the substrate concentrations likely to be present, even in pathological conditions, are considerably less than the K_m of the corresponding enzyme or uptake system. Furthermore, many substrates are vasoactive and may alter blood flow during the process of their metabolism.

A number of methods have been devised to minimize these problems. Low concentrations of substrate have been used, less than the values at which vasoactivity is obvious [33], in addition to synthetic, biologically inactive substrates [122, 134]. A modification of the indicator dilution method yields results independent of flow rate [117] and estimates of Vmax or K_m for the biochemical processes can now be made. These methods have been fully described by their authors [44, 136] and they will not be discussed in further detail here. The methods give essentially the same results from equivalent conditions and, as a first approximation, K_m is taken to represent the "quality", and Vmax, the "quantity" of the endothelial cells.

The effects of flow were recognized in the early work of Fanburg and Glazier [52], who assayed the conversion of AI in dog lung. More recently, the decrease in ACE activity following increased alveolar pressures (10 mm Hg [133]) or produced by respiratory acidosis or alkalosis [134], and that after acute infusion of phorbol ester (PMA) [98] were all attributed to changes in flow or in perfused area. However, injury caused by PMA also affected the quality of the endothelium (K_m) for ACE and for metabolism of 5-HT or AMP [89, 98]. Gross changes in perfused area as a result of embolism or occlusion of pulmonary vessels will also reduce lung metabolic function [59].

Hypoxia was one of the first pathological factors to be investigated for its effects on the metabolic functions of lung. However, the marked vasoconstriction accompanying acute hypoxia introduced a major haemodynamic component into the final result. Attempts to separate haemodynamic from biochemical effects have concluded that the decreased conversion of AI to AII induced by acute hypoxia was attributable largely to haemodynamic changes [32, 131]—that is, changes in Vmax rather than in K_m of ACE activity. Two other observations relate to the haemodynamic changes in acute hypoxia. Inhibition of prostanoid synthesis with indomethacin [14] or antagonism of the effects of EDRF with methylene blue or hydroquinone [28, 93] all potentiated hypoxic vasoconstriction, implying an increased output of endogenous vasodilators in this condition. This possibility is supported by the increased output of vasodilator PGI_2 from cultured endothelium exposed to hypoxic incubation conditions [69], a situation in which haemodynamic effects cannot confuse the issue.

Effect of lung injury. If the pharmacokinetic function of the lung is a normal physiological function, then in abnormal lung, these metabolic functions may also be abnormal and, where morphological modification of the endothelium occurs, such modification should be preceded by a biochemical change. This change should be detectable by measuring the metabolism of an endogenous substrate—that is, a "biochemical index" of lung injury. The hope of finding a reliable biochemical index has been a major purpose in studying the metabolic consequences of several well-established forms of lung injury.

Cardiopulmonary bypass. The iatrogenic lung injury caused by cardiopulmonary bypass (CPB) has been minimized over the years, by improvements in technique. In 1972 Gillis and colleagues [61] found that removal of 5-HT and noradrenaline was decreased following CPB (duration 70–170 min, mean 109 min), but CPB of shorter duration (30–95 min, mean 60 min), as used in 1979, was without effect [60]. In a later series, longer durations (45–190 min, median 88 min) were still without effect on removal of 5-HT [43]. Another substrate affected by CPB was PGE_1, in patients undergoing coronary artery grafting [70] and, in dogs, showing a time-related decrease in metabolism [113]. These metabolic effects confirm that CPB is capable of causing lung injury and that the injury can be minimized by reducing the duration of CPB.

Hyperoxia. Both chronic and acute exposure to hyperoxic environments induce pulmonary vascular injury in which the endothelium is a major site of morphological and functional damage [41]. However, the morphological and respiratory changes take time to appear and an early biochemical warning of impending structural or functional damage has been sought. In a variety of experimental systems, hyperoxia decreases the metabolic function of the lungs towards PGE_2, noradrenaline, 5-HT, bradykinin and AI, at times when the morphological signs of damage have not appeared [14, 45, 59, 62]. In the terminal phase (about 60–72 h for rats) both morphological and biochemical changes are present. It is clear that membrane-associated functions such as the transport system for PGE_2 and the ecto-enzyme ACE, hydrolysing AI and bradykinin, were disrupted in addition to intracellular enzymes such as PGDH. It is important to establish which substrate shows the earliest changes and thus could give the earliest warning of irreversible damage. In one study [135], several substrates were examined and PGE_2 metabolism was the earliest to change; a surprising finding, as PGE_2 is not a substrate for endothelial cell metabolism [14].

Endotoxin and the adult respiratory distress syndrome (ARDS). Many of the lung injury models seek to reproduce the high permeability oedema associated with ARDS. Much of the lung injury following septicaemia appears to derive from the margination and extravasation of activated leucocytes, known to generate oxygen-derived free radicals. A common model of this form of injury uses endotoxin as the injurious agent and has been used widely as an experimental analogue of ARDS [29]. Endotoxin treatment did not affect lung uptake of adenosine [66], a known substrate for endothelial cells, in contrast to decreased uptake after α-naphthylthiourea (ANTU), a selective endothelial cell "toxin" [15]. In rats, endotoxin caused relatively mild injury, measured as lung oedema, but PG catabolism was markedly decreased [66]. This damage was apparent soon (4 h) after the endotoxin was given and before the oedema was detectable. The lung oedema and the metabolic changes were both prevented by treatment with methylprednisolone [78].

The mechanism of the beneficial effect of steroid in this model is unlikely to be via inhibition of PG synthesis, as prostanoid release was not decreased but, surprisingly, PGI_2 output was increased [79]. This result is compatible with others, suggesting that the beneficial effects of steroids in ARDS and ARDS models are not necessarily related to an inhibition of PG synthesis [35, 68, 90, 116].

The metabolic function of lung in patients with confirmed ARDS has been assessed using 5-HT, PGE_1 and propranolol as test substrates. Although uptake of both 5-HT and propranolol decreased, the decrease in 5-HT was better correlated with the severity of ARDS [96]. Two studies used PGE_1 [40, 63], which is metabolized extensively by lung (90% on a single pass). In one group, PGE_1 was given as a therapeutic agent to reduce platelet aggregation and to dilate the pulmonary circulation [40]. In both sets of patients, ARDS caused a decrease in metabolism of PGE_1, but not always with a correlation between severity of respiratory failure and metabolic deficiency. It is nevertheless interesting that one patient "at risk" of ARDS showed decreased metabolism before clinical ARDS was present [40]. It is also encouraging that decreased PG metabolism in ARDS was predicted from experimental work [9, 65]. More clinical studies are required to establish the feasibility of the procedures and, particularly, to extend their use to those *at risk* of ARDS, because it is in this group that a biochemical "early warning" will have the greatest influence on treatment and outcome.

Other forms of lung injury. Many models of lung injury have been devised, some with effects primarily on endothelium (ANTU, early stages of monocrotaline and bleomycin toxicity and oxygen radical generating systems [21, 58]) and others with early or major effects on the epithelium (paraquat, *O*,*S*,*S*,-trimethyl phosphorodithioate (OSS-Me) [102, 127]). The results from these models show a good correlation between endothelial damage and metabolic dysfunction for substrates metabolized by the endothelium. The metabolic changes usually preceded the endothelial cell damage assessed histologically or by oedema. Selective injury to alveolar epithelium (paraquat and OSS-Me) spared the substrates metabolized by endothelium (5-HT, AI [127]), but decreased the uptake of putrescine associated with these cells [102].

PULMONARY PHARMACOKINETICS OF EXOGENOUS SUBSTRATES

There are two major differences in the fate of endogenous and exogenous (drug) substrates in lung. First, the majority of the exogenous substrates removed by passage through the pulmonary circulation are not metabolized, but are simply bound more or less reversibly to some component of lung tissue. The lack of metabolism is not the result of a lack of enzymic activity. Although lung contains less of the mixed function oxidases, demethylases, hydrolases, *etc.* required for drug metabolism than are present in the liver (per gram of tissue), it has enough to metabolize the drugs that are bound [21]. There must be, as for histamine or adrenaline, a lack of access to the necessary enzyme from the pulmonary circulation. This may be because the enzymes are located in the airways, for example in the Clara cells, and the binding sites are endothelial or close to the pulmonary vascular bed, but this point has not been directly investigated.

The second major difference is represented by the airways. For endogenous substrates, entry into the lung via the airways is comparatively rare; aerosolized adrenaline would be one such example. However, exogenous substrates, especially inhalation anaesthetics, are more frequently administered via the airways and, in these instances, metabolism of the substrate is more likely. Isoprenaline absorbed from the airways was metabolized by lung, but it was not taken up from the pulmonary circulation [22, 64]. Beclamethasone given intratracheally to rat perfused lungs was about 50 % metabolized in 2 min when over 95 % of the steroid was still in the lung tissue [71]. However, another similarly used steroid, budesonide, did not show any metabolism in the same system [124]. Both these steroids did exhibit an affinity for lung tissue and were retained within the lung during the perfusion. The ideal bronchodilator or anti-asthmatic steroid should be either bound very strongly to lung tissue or metabolized very extensively within the lung, thus minimizing the possibility of extrapulmonary side effects.

The ideal inhalation anaesthetic must pass freely between air and blood and here a *minimum* of metabolism and binding would be required. For methoxyflurane, the oxidative enzymes in lung are as effective as the hepatic enzymes in producing fluoride [24], but enflurane is not metabolized [25]. Halothane was metabolized by lung microsomes, but at 30 % of the rate of metabolism by hepatic microsomes [25]. Other anaesthetic drugs such as pentobarbitone [85] or alphaxalone [103] are metabolized in lung, but too slowly to be of clinical significance.

Characteristics of drug binding

The sites of drug binding in lung are not clearly defined. Part of the binding of neuronal Uptake$_1$ inhibitors (tricyclic antidepressants) must be to the endothelium, so that the monoamine uptake can be disrupted, and a part elsewhere, in competition with other basic drugs. Similarly, drugs like chlorphentermine must be bound partly to the epithelial cells where they can induce phospholipidosis [21, 30]. The pulmonary toxicity of the antiarrhythmic drug, amiodarone, which has some features in common with phospholipidosis [49], has been correlated with its extensive binding to lung [31].

Drug binding in lung does not appear to be particularly specific. The drugs most effectively bound to lung are amines with $pK_a > 8.0$ and with high lipophilicity [21]. Although quaternary ammonium salts are highly basic, they have low lipophilicity and are not bound by lung [115], but the quaternary herbicide, paraquat, is an exception (see later). A correlation between pK_a and lung binding was shown for local anaesthetics [115] and, in a group of β-adrenoceptor antagonists, the more lipophilic (propranolol and oxprenolol) were more extensively bound [74]. Among analgesics, the less lipid soluble, lower pK_a morphine is hardly affected by passage through human lung (4 % uptake), but more lipophilic drugs with higher pK_a, such as pethidine and fentanyl, are extensively (65–75 %) taken up on first passage [119]. Alfentanil is less avidly taken up (56 %) and both alfentanil and fentanyl are eluted from lung within 10 min after a drug bolus [132].

The lack of binding specificity can also be demonstrated by competition and hence displacement of bound drug by a different drug; imipramine and chlorpromazine or amphetamine [21], lignocaine and bupivacaine or nortriptyline [115]. Apart from isolated lungs and from animals *in vivo*, competitive displacement of drugs has also been demonstrated in man. The first pass lung uptake of an i.v. bolus of propranolol was 75 % but, in those already taking propranolol by mouth, uptake was reduced to about 35 % [56]. In anaesthetized patients, mepivacaine bound to lung was displaced by a bolus of lignocaine [80]. The avid first pass binding of fentanyl (82%) was decreased to 53% in patients already taking propranolol [118]. A more significant measure than uptake is survival—that is, what emerges in pulmonary venous blood. In the last case, fentanyl survival was increased from 18% to 47%, an almost three-fold increase in drug entering the systemic circulation.

The existence of a pharmacokinetic buffer in the pulmonary circulation is both a benefit and a disadvantage. For instance, it would prevent a sudden increase in the venous concentration of a local anaesthetic agent being transmitted directly to the systemic circulation in the heart and CNS. Such increases might result from inadvertent i.v. injection or premature release of tourniquets during regional anaesthesia. On the other hand, the buffering capacity of lung makes it more difficult to estimate the i.v. dose required to achieve a certain antiarrhythmic effect as the binding sites in lung would remove much of the drug until they were saturated and, then, a comparatively small increase in dose would bring about a relatively large effect. For drugs with a less immediate effect, avid binding to lung will clearly affect the arterial blood concentrations after i.v. injection, converting a bolus into a short infusion as the bound drug slowly elutes from the lung, over several circulation times. It will also affect the overall pharmacokinetics if the lung is not in circuit when the drug is given, for example during CPB, and again when the lung is reintroduced at the end of the bypass.

The competition between basic compounds for binding (drug metabolites can bind better than their precursors [31]) creates the possibility of drug interactions analogous to the more familiar examples with drug binding to plasma proteins. The magnitude of these effects has already been demonstrated above for fentanyl [118] and such interactions may be more unrecognized than non-existent.

Factors affecting drug binding

Modulation of drug binding has been studied in a number of conditions. Competition with other blood-borne drugs has already been discussed, but a slightly different interaction is between an inhaled anaesthetic agent and bound drug. Surprisingly, propranolol binding in dog lung was increased during exposure to halothane [108] and lignocaine increased propranolol binding to rat lung [48]. It is possible that the membrane disturbance caused by anaesthetic agents also exposes additional binding sites for basic drugs. It would be useful to discover if the binding of other basic drugs to human lung *in vivo* were similarly affected by i.v., inhalation or local anaesthetic agents.

Lung injury can affect drug binding. Reduction of the perfused vascular bed by vessel ligation, occlusion with a balloon or embolism may cause a decrease in first pass uptake (removal) of propranolol [42, 94, 106], as does experimental atelectasis in dogs [42]. More direct insults to endothelium, such as shock lung in dogs [106] or damage from phorbol esters in rabbit lung [94], decreased propranolol binding. In humans, emphysema [107], postoperative atelectasis [43] and confirmed ARDS [96] all depressed the first pass uptake of propranolol. However, comparisons between 5-HT and propranolol as test substrates for lung injury led to the conclusion that 5-HT was a more useful index of endothelial health [43, 94, 96].

Propranolol seems better able to detect total available surface area (perfused area) than the metabolic quality of the endothelium. Another exogenous amine that may be an index of available area is an iodobenzyl propane diamine (HIPDM). This amine was very strongly bound to isolated lung, but was open to competition by other basic drugs [126]. The compound can be readily labelled with radioactive, γ-emitting, iodine isotopes allowing non-invasive assay and, instead of measuring the uptake by lung, the efflux of bound amine has been monitored. The efflux was slow and biphasic, the two $T_{\frac{1}{2}}$ values being measured in minutes and hours, respectively, and efflux from lungs of smokers was slower than from non-smokers' lungs [111]. This observation suggests that other forms of lung injury may also show differences in HIPDM efflux, offering another possible substrate for the biochemical index.

It is worth reiterating at this point that the location of drug binding in lung is not known and it will include a variable proportion of non-endothelial cells. Because of this uncertainty, it is unlikely that binding of propranolol (or that of any other drug amine) could measure endothelial cell integrity or quality as effectively as a more specific substrate such as 5-HT or AI. Nevertheless, binding of drugs by the lung can be an important factor in their overall pharmacokinetics and could also give rise to significant interactions with other drugs or their metabolites.

Paraquat and polyamine uptake

Work on the uptake of the exogenous substrate, paraquat, led to the identification of a new set of uptake systems for endogenous substrates. Paraquat uptake differs from the processes already considered in two important respects: the first pass uptake is very low, although longer term accumulation in lung is extensive and the site of accumulation and irreversible damage is the pulmonary epithelium [127]. Some of the most effective inhibitors of paraquat uptake are the endogenous polyamines, putrescine, spermine and spermidine, and it is now clear that the paraquat uptake system is identical to that of the polyamines [127]. The polyamines are taken up by the epithelial cells (Type I and Type II) rather than the endothelium [102, 144] and uptake is relatively slow; in rat perfused lungs, the single pass uptake of putrescine was about 0.3% at 0.5 µmol litre^{-1}, compared with 80% for 5-HT or adenosine [13, 16, 144]. For this reason, polyamine and paraquat uptake are usually measured in slices of lung, in which better access to the alveolar epithelium is possible. The polyamine taken up is not metabolized for at least 60 min [127] and this lack of biotransformation is another difference between the fate of the polyamines and that of the monoamines in lung.

Recently, another endogenous substrate, cystamine, has been found for this uptake [87]. This sulphur-containing diamine has a K_m of the same order as that of putrescine, but on uptake it is metabolized to the sulphonic acid, taurine. Taurine itself is also taken up by epithelial cells and by macrophages [18, 86]. The physiological importance of these, primarily epithelial, uptake systems is not known, but polyamines may be necessary for repair of epithelial cells through their effect on cell growth [72]. Perhaps they are also involved in protecting the epithelium against oxidative injury from the oxygen in inspired air, as has been suggested for taurine [18, 86].

CONCLUSIONS

The metabolic and pharmacokinetic capacity of the lung is now a well-established, non-respiratory function. It operates on endogenous and exogenous substrates under physiological, pharmacological and pathological conditions. This lung function impinges on almost every part of an anaesthetist's practice. Inhalation anaesthetics interact with the fate of endogenous substrates. Many of the drugs given i.v. are of the type bound avidly and interactively by lung. A predictive biochemical index for ARDS would save time, effort and lives.

The major advances must come from studies with patients and for these the interest and involvement of the anaesthetist is essential. These studies will require a particular blend of respiratory physiology, cardiovascular pharmacology and clinical measurement—a mixture familiar to most anaesthetists. The relevance of experimental results to clinical practice is uncertain, but the inferences drawn are too strong to be disregarded. The only way forward is to test those inferences.

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PULMONARY INFECTION IN INTENSIVE CARE UNITS

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Since the earliest days of organized intensive care, pulmonary infection has been a problem in patients undergoing artificial ventilation of the lungs [43]. Hospital-acquired pneumonia is an important cause of morbidity and mortality among Intensive Care Unit (ICU) patients, and its incidence has not been reduced by developments in medical technology.

Pneumonia in artificially ventilated patients can be clinically indistinguishable from non-infective conditions commonly encountered in intensive care, such as atelectasis and pulmonary oedema, and the patient's condition may fail to improve even when antimicrobial therapy is commenced early in the course of the condition.

The practical difficulties of diagnosing and treating pneumonia in patients undergoing artificial ventilation have encouraged a more detailed investigation of the determinants of nosocomial pneumonia in the hope of developing more successful preventive strategies. The outcome of this research has been the recognition of the importance of bacterial colonization of the ventilated lung, which in turn has become the basis for preventive strategies, including selective decontamination and preservation of the "gastric acid barrier".

EPIDEMIOLOGY

Hospital-acquired (nosocomial) pneumonia is the third most common category of nosocomial infection, after urinary tract and wound infections, and is more common in the ICU [18]. However, nosocomial pneumonia is claimed to cause more deaths than any other type of nosocomial infection [47]. It is more common in patients requiring mechanical ventilation, which one large study found increased the risk of developing pneumonia by a factor of 21 [29].

There is some confusion as to the terminology used to describe nosocomial pneumonia in intensive care patients. Some authorities have used the terms "primary" and "secondary" synonymously with community- and hospital-acquired in this context, with primary taken to mean pneumonias occurring within 24–48 h after admission to intensive care, and secondary pneumonias occurring thereafter. It should be apparent that a patient could be admitted to intensive care with a pneumonia that developed after hospital admission. To avoid the problem of wrongly categorizing this type of patient, it is better to use the terms "community-acquired" and "hospital-acquired" (nosocomial) pneumonia. In the case of a patient developing pneumonia more than 24 h after commencing mechanical ventilation, it is best to use the term "ventilator-associated pneumonia".

Aspiration pneumonia, or pneumonia developing as part of an aspiration syndrome, may fall into any of the above categories and has its own distinct microbiological features.

The problem of agreeing on common diagnostic criteria for nosocomial pneumonia, and local variations in intensive care admission patterns, means that there is considerable between-centre variation in the stated incidence of ventilator-associated pneumonia. In the United States, baseline epidemiological data have been collected from a representative cross section of hospitals since 1970 in the National Nosocomial Infection Survey (NNIS). An agreed definition has been used for clinical diagnosis of nosocomial pneumonia [47] (in patients without prior pulmonary disease the production of newly purulent sputum more than 48 h after hospital admission, and in patients with prior pulmonary disease increased sputum production and a new onset of pyrexia), but information on subgroups such as ventilator-associated pneumonia has not been collected. The

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overall incidence of nosocomial pneumonia found by the NNIS was 5 per 1000 patients discharged (including deaths). Further epidemiological analysis of these patients since 1974 in the Study on Efficacy of Nosocomial Infection Control (SENIC) found an incidence of 6 per 1000 admissions [28].

The data available on the epidemiology of nosocomial pneumonia in the United Kingdom are limited. A large-scale point prevalence survey was conducted in 1981 by the Hospital Infection Society [39]. An agreed definition of nosocomial pneumonia was used (onset after hospital admission, clinically evident reaction or subclinical reaction; and new purulent sputum or increased sputum; and chest signs or changes in chest x-ray) which differed from the criteria used in the American survey, and did not differentiate ICU patients. Hospital-acquired pneumonia developed in 4.7 patients per 1000 and in only 25% of these patients was a potential bacterial pathogen isolated. While there are many reasons why a bacterial pathogen might not have been implicated, the authors of the above report drew particular attention to the poor correlation between clinical and microbiological diagnosis in nosocomial pneumonia.

The mortality rate in patients with nosocomial pneumonia is high, but there are wide variations in the figures reported. In one study, a mortality rate of 55% was recorded in ventilated patients acquiring pneumonia. However, the same study failed to implicate pneumonia as a significant independent risk factor for ICU mortality after stepwise logistic regression analysis [16]. Another study found a mortality rate of 33% in patients with Gram-negative pneumonia, compared with 3.8% in a control group [51]. Nosocomial pneumonia is thought to be the direct cause of death in 19000 American patients each year, and a contributory factor in a further 58000 [26].

Nosocomial pneumonia adds to the cost of inpatient care by prolonging the period during which ventilatory support is required, generating a series of additional diagnostic procedures and increasing consumption of expensive therapeutic agents—in particular, i.v. antibiotics. The additional expenditure attributed to the estimated 1.3 million nosocomial pneumonias in the United States each year is about $1 billion at 1985 rates. If the SENIC estimate that 17% of all nosocomial pneumonias are ventilator-associated is correct [29], the annual estimated attributable cost of ventilator-associated pneumonia in the U.S.A. alone would be greater than $170 million. The true figure is likely to be higher than this, because of the rising cost of health care and the increasing incidence of nosocomial pneumonia (thought to be the result of increasingly ambitious medical intervention).

The data required to produce detailed costings for the consumption of resources attributable to pneumonia in intensive care patients are not available in the U.K., but since the cost of treatment with a single injectable antibiotic for one patient may be several hundred pounds, and every day spent in an ICU costs approximately £500 [49], it is certain that pneumonia represents a considerable drain on health care resources, probably running to an annual total of many millions of pounds.

DIAGNOSIS

An aetiological diagnosis may already be available in cases of pneumonia acquired before admission to the ICU. When this information is not available, a full diagnostic investigation (including sputum and blood culture) should be completed before commencing antimicrobial therapy. Where viral, mycobacterial or atypical pneumonia is suspected, it is advisable to take the appropriate specimens as soon as possible after the patient's admission to the unit, since diagnostically useful information may not be available for several weeks. When pneumocystis pneumonia is suspected, specimens should be obtained at bronchoscopy, preferably by broncho–alveolar lavage [23].

The diagnosis of ventilator-associated pneumonia is complicated by the insidious and non-specific nature of its clinical presentation, and by the common finding of a colonizing bacterial flora in the trachea and upper bronchi. These diagnostic problems mean that a close collaboration between clinical and laboratory staff is required.

Bacteria isolated from the smaller airways are presumed to be of greater aetiological relevance to current pulmonary infection than isolates from the trachea and main bronchi. While the presence of a tracheal tube bypasses the principal source of contamination of sputum specimens, bacterial colonization of the trachea will confound attempts to obtain specimens when a standard bronchoscopy specimen brush is used. To overcome this problem, a protected specimen brush was developed, with a double-lumen catheter. The sensitivity was found to be high when a threshold of $> 10^3$ bacteria per 1 ml of secretions was used as a cut-off point for bacterial counts in specimens recovered using this device in animals [40]. However, a study using the protected specimen brush in ventilated human subjects and the same quantitative threshold showed that false positive results were common, and found a selectivity of 42% [13]. The sample brush used for specimen collection has been improved by the addition of a small agar plug, which can be dislodged after placement of the device.

Quantitative bacteriological analysis of secretions obtained with the protected specimen brush does not provide clinically useful information in time to affect initial therapeutic decisions, as it depends on the results of culture. Moreover, the technique also relies on accurate placement of the bronchoscopy catheter. Another approach relies on Gram staining of cytocentrifuged broncho-alveolar lavage fluid to demonstrate intracellular bacteria, and has the advantage of producing results in time to influence therapeutic decisions. One study comparing the protected specimen brush technique with broncho-alveolar lavage in patients undergoing artificial ventilation of the lungs found similar degrees of accuracy [12].

Alternative, more invasive techniques, such as percutaneous needle aspiration and transbronchial biopsy, may have a role in diagnosis of pulmonary infections in ICU patients, but the potential for serious complications such as pneumothorax means that this is strictly limited. Open lung biopsy has been recommended for diagnosis of pulmonary infections in immunocompromised patients, and the available data suggest that there is a higher diagnostic yield than with transtracheal biopsy. However, the results of biopsy often do not warrant a change in treatment, and mortality rates do not appear to be altered by the information generated.

The diagnostic techniques used in most centres do not produce results quickly enough to influence the choice of antibiotics when treatment is urgent. Until diagnostic methods allow more accurate diagnosis, particularly a confident negative diagnosis, of pneumonia in the patient with ventilated lungs, the appropriateness of antibiotic therapy will remain a largely retrospective judgement.

A practical approach to the intensive care patient with suspected pneumonia would be:

(1) Spontaneously ventilating, with productive cough: microscopy and culture of sputum.

(2) Spontaneously ventilating, without productive cough: chest physiotherapy, and consider transtracheal aspiration if this fails to produce a sputum specimen.

(3) Mechanically ventilated, onset within 48 h of admission: check for recent sputum and blood culture reports. Obtain sputum and blood culture specimens, and request urgent Gram stain on sputum.

(4) Mechanically ventilated, onset 48 h after admission to ICU or later: preferred method of diagnosis is quantitative culture and cytological examination of broncho-alveolar fluid specimens if the laboratory has experience of these techniques. Culture of sputum obtained by tracheal suction may establish bacterial colonization of larger airways, but will not distinguish between colonization and infection. If clinical picture unresolved when results available, discuss interpretation and therapeutic strategy with microbiologist.

(5) Clinical picture suggests atypical pneumonia: collect 10 ml of blood as first in pair of specimens for serological analysis.

(6) Patient with AIDS or otherwise immunocompromised: discuss possibility of *Pneumocystis carinii* with microbiologist and obtain specimen for immunofluorescent stain by broncho-alveolar lavage or, preferably, bronchoscopic biopsy. Consider possibility of tuberculosis or cytomegalovirus pneumonia in AIDS patient. Discuss with microbiologist if special diagnostic procedures are required, for example for atypical mycobacteria.

AETIOLOGY

It is rarely possible to predict the bacterial pathogen responsible for pneumonia in the intensive care patient because any one of a wide range of species may be involved. In patients admitted to ICU with community-acquired pneumonia, common respiratory pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae* are often isolated. The results of a large scale survey of community-acquired pneumonias are listed in table I. *Mycoplasma pneumoniae*, *Legionella* sp., and the recently identified TWAR strain (so-called after the first strain isolated: Taiwan, adult respiratory) of *Chlamydia* [25] may also be implicated if the appropriate investigations are carried out. As yet, the necessary diagnostic

TABLE I. *Agents of community-acquired pneumonia.* (*Taken from a prospective survey* [2])

Microbial agent	No.	%
Streptococcus pneumoniae	154	34
Mycoplasma pneumoniae	81	18
Influenza A virus	32	7
Haemophilus influenzae	26	6
Chlamydia psittaci	13	3
Legionella pneumophila	9	2
Streptococcus, other species	6	1
Coxiella burnettii	5	1
Staphylococcus aureus	5	1
Enterobacteriaceae	4	1
Others	8	2
Microbiologically negative	150	33

TABLE II. *Bacterial species isolated in association with nosocomial pneumonia.* (*From the National Nosocomial Infection Survey, 1980–1982* [47])

Bacterial species	%
Pseudomonas spp.	15
Klebsiella spp.	14
Staphylococcus aureus	14
Enterobacter spp.	10
Escherichia coli	8
Haemophilus influenzae	8
Proteus spp.	7
Morganella morganii	
Providencia stuartii	
Serratia marcescens	6
Streptococcus pneumoniae	4
Streptococcus faecalis	2
Other Gram-positive spp.	5
Anaerobic spp.	< 1
Miscellaneous spp.	3

tests are available in only a few centres. Tuberculosis is seen rarely outside the major at-risk groups, but is commonly found in patients with AIDS, from whom atypical mycobacteria, such as the avium-intracellulare group, may be isolated. Patients whose immune system is compromised by AIDS or other factors are at risk from pneumonias caused by opportunist organisms such as *Pneumocystis carinii*, and cytomegalovirus, in addition to more common bacterial respiratory pathogens.

After aspiration of gastric contents, bacteria may play a secondary role in causing pulmonary damage, or may cause an invasive infection where pulmonary tissues have already been disrupted by prior chemical or mechanical damage. The bacterial species commonly associated with aspiration pneumonia are similar to those normally found in the bacterial flora of the oro- and nasopharynx, including penicillin-sensitive anaerobic species [5]. In our centre, *Staphylococcus aureus* has been isolated in a number of severe pulmonary infections following aspiration.

The microbial species associated with hospital-acquired pneumonia (table II) differ from those associated with community-acquired pneumonias in several respects. Viral and anaerobic bacterial species are rarely implicated, and common bacterial respiratory pathogens are isolated less frequently than Gram-negative species, which explains why some authors refer to nosocomial pneumonia as "Gram-negative pneumonia".

The Gram-negative species isolated from patients with nosocomial pneumonia are divided by some authorities into "endogenous" and "exogenous" groups, according to the presumed source of the organism. Typical exogenous species include *Pseudomonas aeruginosa* which is a common contaminant of the hospital environment, and not a major component of the normal human microbial flora. Representative endogenous species would include *Escherichia coli*, which is commonly found in the human intestinal flora.

The rigid subdivision into exogenous and endogenous groups is probably no longer appropriate, because of changing views on the principal mechanisms of respiratory colonization and the observation that even species classically regarded as exogenous in origin, such as *Pseudomonas aeruginosa*, may become transient members of the gastrointestinal flora in some ICU patients [1].

There is some evidence that the newly recognized *Chlamydia* TWAR strain has been a cause of nosocomial pneumonia in a number of patients [24], but too little is known about this organism at present to permit comment on its importance in ICU patients.

There have been a number of outbreaks of nosocomial legionnaire's disease documented since the species was first recognized in the late 1970s. One outbreak affected patients in the high-dependency peripheral vascular and cardiothoracic unit of the Glasgow Royal Infirmary and was caused by spray from a wet cooling tower entering the closed ventilation system to the unit [55]. This particular outbreak might have been prevented had the first case, which was 6 weeks earlier than the others and proved fatal, prompted an investigation of the air conditioning system.

Respiratory colonization

The presence of bacteria in the lower respiratory tract is an abnormal finding which, in spontaneously ventilating patients, would normally be associated with a pathological process such as chronic bronchitis or cystic fibrosis [35]. In artificially ventilated patients, the architecture of the respiratory tract is altered by the presence of the tracheal tube so that bacteria are commonly found in the larger airways. Although it may be possible theoretically to distinguish between bacteria that are merely colonizing the lower respiratory tract and those causing infection, this is rarely possible in clinical practice.

In the patient with the trachea intubated, colonization is important as a necessary precursor to pneumonia, and implies a more than transient association between a given bacterial species and the lower respiratory tract mucosa. The species in question must therefore have found a means of adhesion to host cell surface structures, and a source of substrates for microbial metabolism, whilst avoiding the antibacterial effects of IgA, lysosyme, and bacteriocidins produced by other bacterial species.

The procedures used in most diagnostic laboratories do not attempt to recognize this complex relationship, and can only achieve a crude approximation by demonstrating the presence of bacteriologically identical isolates over a period of time, in the absence of the clinical features of infection.

The interrelationship between colonizing bacteria and respiratory mucosa is further complicated by the mediating influence of respiratory mucus. This viscoelastic liquid is a complex milieu in which a lattice of negatively charged mucopolysaccharide fibrils is surrounded by cations and water molecules. In the presence of inflammation, increased local concentration of cations may change the stereochemical arrangement of mucopolysaccharide fibrils, thus altering the viscoelastic properties of respiratory mucus to make it more tenacious [22]. DNA fibres released into respiratory secretions upon the death of granulocytes also contribute to the increased viscosity of purulent sputum.

The aerobic Gram-negative bacilli most commonly associated with pneumonia in ICU patients are rarely found amongst the bacterial flora of the buccal cavity or pharynx in healthy adults. The frequency with which *Pseudomonas aeruginosa*, a common hospital environment organism, was isolated from ICU patients with pneumonia, and the concurrent isolation of the same species from respiratory support equipment gave credibility to the view that bacteria gained access to the lower respiratory tract via the ventilator circuit. Common-source outbreaks of nosocomial pneumonia as a result of contamination of ventilators and other respiratory support equipment were reported [44]. Despite improvements in equipment design and the introduction of infection control procedures, common-source incidents involving *Klebsiella* sp., *Acinetobacter* sp. and other bacterial species continue to be reported from ICUs [8, 10].

It was first proposed that bacteria colonized the lower respiratory tract of ventilated patients from a source within the patient when a correlation was recognized between bacterial isolates from tracheal secretions and isolates from oropharyngeal specimens. This study also noted that prior treatment with antibiotics increased the risk of development of a Gram-negative lower respiratory flora, as a result of selection pressure on antibiotic-sensitive species [54]. Another factor found to correlate with the acquisition of Gram-negative species in the oropharynx was the severity of illness, irrespective of prior antibiotic treatment [34].

It is now recognized that the systemic effects of severe illness can cause molecular changes in the cells on mucosal surfaces, which in the mouth results in cleavage of fibronectin, causing an increase in available binding sites for Gram-negative bacteria [58]. Surface structures on Gram-negative bacteria, termed pili, adhere to receptor sites on mucosal epithelial cells. Mucosal binding of *E. coli* for example, can be inhibited by prior treatment of the surface with concanavalin A, which binds to mannose [42].

A study in adult volunteers showed that nine of 20 subjects aspirated small quantities of fluid into the trachea during deep sleep [31]. In the same study, aspiration of fluid into the trachea occurred in seven of 10 patients with a reduced level of consciousness. Aspiration occurs frequently in patients with head injury, patients undergoing controlled ventilation and patients treated with sedative drugs.

It is possible that the tracheal tube may, by interfering with deglutition, add to the pooling of secretions in the lower pharynx and upper oesophagus. The inflatable tracheal tube cuff was designed to prevent aspiration of a large fluid bolus into the trachea providing the cuff remained inflated, and modern high volume–low pressure cuffs do not often deflate spontaneously. However, the intentional cuff deflation practised in some ICUs in order to prevent mucosal damage will allow contaminated secretions that have pooled above the cuff to gain access to the lower respiratory tract. Furthermore, bacteria can still gain access to the lower trachea from the reservoir above the cuff by passing between the cuff and the tracheal mucosa when the tube moves in relation to the trachea. This may occur during respiratory care procedures or even in the course of the normal ventilatory cycle.

While this phenomenon is easily demonstrated *in vitro*, it is not possible to demonstrate it directly in patients with the trachea intubated. However, there is indirect bacteriological evidence to support the above sequence of events. In one study of 10 mechanically ventilated patients, gastric bacterial overgrowth was observed in nine, and evidence for a sequence of colonization from stomach to trachea was found in three [4].

Effect of gastric pH on colonization

In a later study of patients undergoing mechanical ventilation, those with a gastric pH greater than 4.0 were found to be at higher risk of gastric bacterial overgrowth, bacterial counts reaching 10^8 ml^{-1} in some patients. Gastric bacterial overgrowth was unusual in patients with a gastric pH less than 3.5. Histamine blockers and antacids were observed to be associated with a greater risk of gastric bacterial overgrowth [41].

The same group isolated Gram-negative bacilli from either or both stomach and trachea in 52 of 58 postoperative patients, claiming a sequence of isolation in 17 of the 52 patients (in 11 of 17 patients with this apparent sequence, gastric colonization occurred before tracheal colonization). Bacterial translocation from the stomach to the trachea of mechanically ventilated patients has been termed "retrograde colonization".

Other studies of gastric bacterial overgrowth in artificially ventilated patients have confirmed these observations, but have not established a direct relationship between gastric colonization and subsequent pneumonia in ICU patients. Indirect evidence to support this relationship came from a study of risk factors for ventilator-associated pneumonia in 233 patients, in which it was shown that the use of histamine type 2 blockers was a significant risk factor for pneumonia [16].

Other explanations are possible for some of the above bacteriological findings. Changes on mucosal surfaces might occur which allow previously suppressed Gram-negative species to grow above the lower limit of detection, or bacteria might gain access to the lower respiratory tract via the circulation following translocation across the intestinal mucosa. While these remain theoretically possible, the observations made in recent clinical studies concur with the "retrograde colonization" model.

The increased risk of respiratory colonization following use of histamine antagonists is thought to be a pH-mediated effect, in which stress ulcer prophylaxis blocks gastric acid secretion, removing the "gastric acid barrier" and thereby promoting the overgrowth of aerobic Gram-negative bacteria in the stomach.

Little information is available on gastrointestinal physiology in patients undergoing mechanical ventilation of the lungs, but clinical experience suggests that a large proportion of patients ventilated for a prolonged period have delayed or absent gastric emptying, whether caused by postoperative ileus or other factors, such as administration of opioids. A static small intestine is likely to assist bacterial overgrowth in the jejunum and duodenum, to produce the contaminated small bowel syndrome [6].

It is assumed that bacteria in the gastric contents gain access to the trachea either by active regurgitation or by passive flow along the oesophagus. The reason why thoracic and upper abdominal operations put patients at greater risk of pneumonia [30] may be a decreased efficiency of anti-reflux mechanisms and, in the case of oesophagectomy, a shortened distance between pooled gastric contents and epiglottis. Reflux of gastric contents is also assisted in artificially ventilated patients by the presence of the nasogastric tube, which keeps the oesophagus open, allowing fluid to pass along its outer surface, and by the near-horizontal positioning of most ICU patients.

Mucociliary clearance

Under normal physiological circumstances, micro-organisms that impinge on mucosal surfaces in the lower respiratory tract are trapped in respiratory mucus and cleared by the continuous upward movement of the mucus layer caused by cilia on the epithelial surface. Larger particles and boluses are cleared by the cough reflex. In artificially ventilated patients the tracheal tube presents an anatomical barrier to upward mucociliary movement at the level of the inflatable cuff. Respiratory secretions build up in the region of the tube tip. The tracheal mucosa may be damaged by contact with the tracheal tube or the suction catheter tip, even at low suction pressures [46]. There is experimental evidence from work on ferrets that mechanically induced damage to the tracheal mucosa assists the adherence of *Pseudomonas aeruginosa* by exposing areas of basement membrane [45]. It is possible, therefore, that the local inflammatory reaction seen in the intubated trachea during prolonged ventilation may begin with mechanical damage and proceed to a low grade bacterial insult.

Colonization from tracheal tube biofilm: two phase flow

Spread of bacteria into the lungs of ventilated patients cannot be explained by retrograde colonization alone, for this model of bacterial spread only provides for the carriage of bacteria as far as the trachea. It has been observed that a film of bacteria and respiratory secretions form on the inner surface of tracheal tubes during prolonged use [50]. It was proposed that fragments of this biofilm could be dislodged during insertion of the suction catheter, and carried further into the lung.

Further investigation of this tracheal tube biofilm, including flow studies with tubes removed from patients undergoing artificial ventilation, has shown that small fragments of biofilm can be disseminated by ventilator gas flow. Scanning electron microscopy and bacteriological studies of filters used in ICU ventilator circuits revealed particles consistent with dissemination of tracheal tube biofilm during the expiratory phase of ventilation *in vivo* [33]. Particles produced in this system have been found to be as small as 25 μm [32], and have been shown to travel up to 90 cm. Additional gas–liquid interaction with the layer of respiratory mucus lining the lower trachea is possible, but since the tracheal tube has a narrower diameter, it is probably the zone of maximal gas–liquid interaction and biofilm fragmentation. Furthermore, it is known that gas–liquid interaction may occur at relatively low Reynolds numbers, although this may be sufficient only to cause flow of the biofilm layer, without fragmentation and subsequent particle dissemination [14].

The local inflammatory reaction discussed above ensures that activated neutrophils are present in the material on the inner surface of the tracheal tube. Gas–liquid interaction may therefore disseminate into the lung host-derived inflammatory mediators such as myeloperoxidase and neutrophil elastase.

The probable explanation for the formation of a biofilm on the inner surface of tracheal tubes is that respiratory secretions are propelled into the mouth of the tracheal tube after accumulating below its tip. This material is probably carried further into the tracheal tube, and smeared over the inner surface by passage of the suction catheter.

Hypothesis for bacterial colonization of the ventilated lung

The patient has an abnormal gastrointestinal flora at or shortly after admission to the ICU, and diagnostic and therapeutic procedures used during admission may cause further alterations in that flora. Overgrowth of Gram-negative species in the stomach contents is the result of increased gastric pH. Reflux of gastric contents carries bacteria into the respiratory tract. Bacteria from the stomach and oropharynx accumulate above the inflatable tracheal tube cuff and pass in small quantities to contaminate the respiratory secretions accumulating below the cuff. Mucociliary clearance and passage of the suction catheter through these secretions leads to the development of a biofilm on the inner surface of the tracheal tube and the larger airways. When the biofilm reaches sufficient thickness, gas–liquid interaction causes fragmentation of the biofilm surface and dissemination of bacteria-laden particles deep into the lung. Bacterial components and host-derived inflammatory mediators then initiate the damage that produces the clinical features recognized as ventilator-associated pneumonia (VAP).

Bacteria–host interaction

Bacteria–host interaction is of the utmost importance in the foregoing hypothesis, and the aerobiology of inhaled micro-organisms appears to be a major factor in the development of disease. It was not recognized until recently that the method of administration of bacteria to experimental animals was an important factor in determining the host response.

Experiments on mice have shown that the response to inhaled *Streptococcus pneumoniae* depends on whether they are delivered as an aerosol of monodispersed organisms, or as a cloud of aggregated bacteria [3]. When bacteria are inhaled in the aggregated form, a smaller inoculum was observed to cause saturation of the pulmonary macrophage system and induction of a neutrophil response. These observations have been repeated with a variety of bacterial species relevant to pulmonary infection in humans, including *Pseudomonas aeruginosa* [9]. It appears that aggregated bacteria are more resistant to phagocytosis than are monodispersed organisms. It has been claimed that the biofilm also gives bacteria some resistance to phagocytosis [48]. The size of biofilm particles produced by gas–liquid interaction means that only a small percentage may reach the smallest airways compared with an aerosol of monodispersed bacteria, yet their resistance to phagocytosis may render such particles more pathogenic.

Although the "retrograde" route from the patient's own gastrointestinal tract is currently favoured as the principal means of respiratory colonization, the more direct route from external sources in respiratory support devices is still believed to account for a proportion of pneumonias in ICU patients.

Role of host factors

Host factors that increase the risk of pneumonia, such as pre-existing pulmonary disease, operative procedures and smoking, have already been mentioned. In the immunocompromised patient, host factors are an even more important determinant of pneumonia, increasing the susceptibility of the lower respiratory tract to infection by common respiratory pathogens and opportunist organisms. The pulmonary infections to which an immunocompromised patient is more susceptible differ with the nature of the compromise. For example, a patient with deficient cell-mediated immunity as a result of AIDS, a lymphoma, an organ transplant or steroid treatment is at increased risk of cytomegalovirus, pneumocystis, cryptococcal, and nocardial infections, while a neutropenic patient is at increased risk of Gram-negative, staphylococcal and fungal infections.

TREATMENT

Once the presumed cause of bacterial pneumonia has been identified, the appropriate antimicrobial agent may become clear before antimicrobial susceptibility results have become available. In many cases, susceptibility data will be obtained too late to influence urgent therapeutic decisions. We have found that a planned progressive antimicrobial prescribing policy can be applied to the majority of intensive care patients with pneumonia.

Ampicillin is used to treat community-acquired bronchopneumonia, with erythromycin in reserve for patients with a documented penicillin allergy. Erythromycin is used for patients with a suspected community-acquired atypical pneumonia caused by either *Legionella pneumophila* or *Mycoplasma pneumoniae*. When a patient has a lobar pneumonia, or when *Streptococcus pneumoniae* has been isolated, i.v. benzyl penicillin should be used in preference to other penicillins. We use i.v. cloxacillin to treat patients with staphylococcal pneumonia following influenza and often, in our experience, aspiration of gastric contents. The more severe cases of staphylococcal pneumonia usually require the addition of fucidic acid.

In cases of aspiration pneumonia we use ampicillin, although there is no convincing evidence that antibiotics significantly alter the course of the disease. In our experience, the most problematic agent of secondary infection following aspiration has been *Staphylococcus aureus*, for which the appropriate antibiotic is cloxacillin, with the possible addition of fucidic acid, as described above. Some centres use metronidazole, although most oral anaerobic bacteria are penicillin-sensitive.

Our first choice for a patient with VAP occurring more than 48 h after admission to the ICU is cefotaxime. When gentamicin is used to treat Gram-negative pneumonia, it should be accompanied by another agent because of its poor bioavailability in respiratory secretions. When the patient is known to have a *Pseudomonas aeruginosa* pneumonia we use either a combination of gentamicin and piperacillin, or ciprofloxacin alone. Changes to the type and duration of antimicrobial chemotherapy are normally made after discussion with a microbiologist and consideration of current microbiological data.

In many ICUs, a large proportion of patients have already been given antibiotic treatment before their admission to the unit. To prevent the accumulation of antimicrobial resistance and to reduce selection pressure caused by widespread use of systemic antimicrobial agents, it is wise to review all surgical antibiotic prophylaxis regimens on admission of the patient to the ICU, aiming to discontinue such prophylaxis after a maximum of 48 h. If antibiotics are required for therapeutic purposes, different agents should be used.

In most ICUs the i.v. route of antibiotic administration is used for treatment of patients with pneumonia. Therapeutic concentrations are obtained rapidly and the widespread use of intravascular lines makes this route convenient. Despite promising early claims [37], intrabronchial administration of antibiotics in the treatment of VAP has not been shown to be superior to more conventional routes of administration. Moreover, problems of early antimicrobial resistance have been reported in patients treated with intrabronchial antibiotics [21].

Other therapeutic measures

Maintenance of adequate oxygenation and physiotherapy are a common adjunct to antibiotic treatment of pneumonia in ICU patients. Physiotherapy in VAP has been poorly researched and there is limited evidence for a specific beneficial effect.

The suction catheterization that accompanies chest physiotherapy or is carried out independently may be administered as frequently as every 30 min, with the possible consequences of mucosal damage, bacterial colonization, tracheal tube biofilm formation and bacterial contamination of the lung.

PREVENTION

A number of preventive strategies have been designed to deal with the problem of VAP.

Equipment

The earliest attempts to prevent pneumonia in ICU patients involved the disinfection and sterilization of respiratory support equipment such as ventilators and ventilator tubing. Further measures included the use of sterile water in humidifier reservoirs and sterile charging solutions in nebulizers. Recent developments in the "device hygiene" approach have been the introduction of disposable core-heated humidifiers with disposable sterile water reservoirs, and low resistance microbial ventilator filters.

The transmission of bacteria between patients on the hands of staff is facilitated by the need for rapid access in resuscitation procedures and by inadequate staffing levels or high levels of bed occupancy [27]. Infection control in intensive care is assisted by a high staff: patient ratio, in-service training on infection control practice and collaboration with the hospital infection control team.

There is disagreement over the usefulness of microbial ventilator filters. There have been reports of sudden increases in resistance as a result of the accumulation of condensate [7]. Moreover, one study comparing the incidence of pulmonary infection in patients with and without filters as part of their ventilating apparatus, failed to show a significant difference between the two groups [17]. These results possibly reflect the relative importance of the endogenous route of colonization over the exogenous route. The issue of whether or not to use microbial ventilator filters remains unresolved, as the evidence for any measurable benefit is scanty, while the claimed risks of use have not been substantiated in clinical trials.

Where pulmonary infections by *Legionella pneumophila* have been a problem, specific measures have had to be taken by hospital engineers, with particular emphasis on air-conditioning systems and cooling towers.

Bacteriological examination of ventilator tubing to assess the adequacy of policies for replacement or sterilization has shown that the greatest contamination occurs at the patient's end of the tubing, and that the organisms isolated are normally those found in the patient's respiratory tract [15]. These observations are not conclusive evidence for an endogenous source of contamination of ventilator tubing, but they do support the view that the respiratory support equipment is a less importance source of bacterial contamination than the patient. It is therefore possible that microbial filters may have a role in intensive care practice, but as a means of preventing the contamination of tubing rather than in the prevention of pulmonary colonization.

Selective decontamination of the gut

The first major strategy designed to interrupt pathways of endogenous bacterial colonization was selective decontamination of the digestive tract (SDD).

Selective decontamination relies on the concept of "colonization resistance". This concept was developed from work on the intestinal bacterial flora of mice, following problems with unwanted gastrointestinal colonization in gnotobiotic animals. These studies were the foundation for the current belief that the majority anaerobic gut flora hold the minority aerobic Gram-negative species in check, preventing overgrowth of commensal Gram-negative bacteria or colonization by exogenous Gram-negative aerobes [57].

Antibiotic regimens were screened in mice for their effect on the colonization resistance provided by the anaerobic flora, and agents chosen if the anaerobic flora were preserved while the aerobic Gram-negative bacterial and yeast flora were suppressed. From this work a combination of tobramycin, polymixin E and amphoteracin B was chosen. Preliminary trials of these three agents in paste given orally and down the nasogastric tube, combined with cefotaxime given for the first 4 days of the decontamination regimen, in patients who had experienced multiple trauma, were claimed to show a reduction in the incidence of pneumonia from 59% to 8% [52]. In a later study, no significant selection of antimicrobial resistance was found [53].

A number of SDD trials have been conducted, with varying degrees of success and with differing criteria for the diagnosis of VAP.

A detailed study of SDD was conducted over two non-consecutive 6-month periods by a group in Glasgow, using a strict definition of pulmonary infection [36]. The incidence of respiratory colonization and secondary pneumonia decreased in the SDD treated group, although there was no significant reduction in mortality rate in this group. After *post-hoc* stratification, however, a significant reduction in the mortality rate of the multiple trauma subgroup was noted. These results led to the recommendation that SDD should be used only in those ICUs where thorough microbiological surveillance was possible.

Despite the absence of acquired antimicrobial resistance in this and other studies of SDD, misgivings have been expressed concerning the use of prolonged, broad spectrum prophylactic regimens in a group of patients at high risk of carrying a preselected resistant bacterial flora [20]. There is particular concern about cefotaxime, which has been used as a supplementary prophylactic agent in most of the SDD trials to date. Cefotaxime is said to be required as treatment for primary infections established before admission to the ICU, yet the use of SDD regimens without such pre-emptive treatment has not yet been evaluated properly. It is therefore not possible to separate the effects of the SDD agents and cefotaxime on bacterial isolates from clinical samples during the first 4 days of admission to the ICU—the key period during which initial respiratory colonization takes place. Moreover, Gram-negative species producing enzymes capable of inactivating cefotaxime have been reported recently [11]. Extensive use of SDD in ICUs could provide suitable conditions for the selection of resistance and reduce the clinical effectiveness of a hitherto useful agent.

In every SDD trial so far, there has been a proportion of patients who develop secondary or ventilator-associated pneumonia despite rigorous application of the regimen. A possible reason for respiratory colonization during the use of SDD could be a reduced antimicrobial effect in patients with slowed or absent gastrointestinal motility. A large bacterial biomass in the stomach and upper small intestine may reduce the effectiveness of intragastric antibiotics. There is, therefore, a possibility that SDD is more effective at preventing colonization in patients who already have a lower risk of developing pneumonia.

A further point raised by work on SDD is the relationship between VAP and ICU mortality. A significant decrease in mortality should be expected in SDD-treated patients if there is a substantial decrease in the incidence of VAP. The absence of such a relationship in general intensive care patients raises important questions about VAP and whether it is a true pulmonary infection.

When day-by-day microbiological support is available, SDD may have a place in the management of patients requiring ventilatory support for more than 48 h, but only if it is recognized that the benefits may be more subtle than a reduction in mortality. A careful cost–benefit analysis of SDD may clarify this matter.

Sucralfate

Many of the theoretical and practical weaknesses of SDD do not apply to another preventive strategy recently proposed for patients undergoing artificial ventilation. This is preservation of the "gastric acid barrier" by substitution of histamine blocker stress ulcer prophylaxis with sucrose aluminium sulphate (sucralfate). This novel anti-ulcer agent works by coating damaged gastric mucosa, and does not significantly reduce gastric pH [56]. By avoiding the additional risk of respiratory colonization resulting from the gastric bacterial overgrowth caused by reduced gastric acid secretion, it was thought that use of sucralfate would cause a decrease in the incidence of VAP.

In a study of sucralfate compared with antacids or cimetidine in 130 general ICU patients, gastric colonization with Gram-negative species and gastric pH were higher in the group receiving antacids or cimetidine [19]. VAP was reduced from 23 % to 12 % in the sucralfate group, but the difference was not significant unless patients withdrawn from the sucralfate group and given cimetidine by their attending physician were removed from the study. The marginal statistical significance of this study detracts from the apparent trends of reduced colonization and reduced VAP when the gastric acid barrier had been preserved with sucralfate.

The attractions of a sucralfate-based strategy are that it should not select antimicrobial resistance or require microbiological surveillance. It is also simpler to administer. This strategy, like SDD, has a measurable failure rate which is probably attributable to the proportion of intensive care patients who have a high resting gastric pH. There may be reasons for this other than the administration of antacids or histamine blockers for prophylaxis of stress ulcer, which contribute to gastric bacterial overgrowth and will confound attempts to prevent subsequent respiratory colonization by using sucralfate. An antibacterial effect has been claimed for sucralfate [39], but it is unlikely that this has a significant effect on the high concentrations of Gram-negative bacilli found in the stomachs of some patients being ventilated artificially.

CONCLUSIONS

Pneumonia remains an important problem in ICU patients, despite advances in respiratory support and other aspects of intensive care. While the management of community-acquired pneumonia and postoperative pneumonia is often straightforward, management strategies for VAP are still far from satisfactory.

Difficulties with diagnosis and conventional antimicrobial therapy in VAP have led to the development of new diagnostic techniques such as broncho–alveolar lavage and the bronchoscopic protected specimen brush, and preventive strategies such as selective decontamination and sucralfate-based preservation of the gastric acid barrier.

Many improvements could be made to the management of pulmonary infections in the ICU, but a number of issues, such as the contribution of altered gastrointestinal physiology, tracheal suction procedures and bacterial–mucosal interaction, still require resolution.

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THE ADULT RESPIRATORY DISTRESS SYNDROME: DEFINITION AND PROGNOSIS, PATHOGENESIS AND TREATMENT

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The Adult Respiratory Distress Syndrome (ARDS) was first described in a British journal by Ashbaugh and colleagues [3] more than 20 years ago. Since that time, a considerable body of knowledge about ARDS has emerged from both clinical and experimental work, but much more needs to be learned about the basic mechanisms that regulate the initial inflammatory response, and about the factors that regulate the repair process in the lung.

This review has four objectives. First, we will critically examine the classic definition of ARDS and determine whether an expanded definition would provide a more workable approach for determining prognosis and guiding therapy for patients with acute lung injury. Second, although the pathophysiology of ARDS has been well described, we will review a number of new developments in our understanding of the extent of lung and pleural involvement in ARDS. Third, both clinical and experimental studies have provided a long list of possible mechanisms that could be responsible for the pathogenesis of acute lung injury in man. We shall review some of the most promising developments in both clinical and basic research that shed new light on the mechanisms of acute lung injury and repair. Our final objective will be to review the status of current treatment for ARDS and to discuss new treatments that may become available in the next few years.

DEFINITION, EPIDEMIOLOGY AND PROGNOSIS OF ARDS

In 1967, Petty described ARDS as a syndrome of acute respiratory failure characterized by non-cardiogenic pulmonary oedema with severe hypoxaemia caused by right-to-left intrapulmonary shunting secondary to atelectasis and air space filling from oedema fluid [3]. The chest radiograph showed diffuse pulmonary infiltrates, and there was a decrease in lung compliance; the lungs required higher than normal airway pressures to inflate them to a normal tidal volume.

Although this clinical description was very useful, there is now a need for a more comprehensive definition. First of all, the heterogeneity of both the inciting clinical disorders and the variability of the clinical course of ARDS has been better appreciated. For example, the importance of non-pulmonary organ failure, independent of respiratory failure, has been recognized increasingly as a major cause of death in patients who develop acute lung injury. Also, the prognosis for recovery depends on the associated clinical disorder: ARDS associated with sepsis has a 90% mortality, while ARDS associated with fat embolism has a 10% mortality.

The incidence of ARDS has been difficult to establish. In 1977, it was estimated that there were 150000 cases of ARDS annually in the United States with a mortality of approximately 50–60% [80]. Recently, Webster, Cohen and Nunn reported a much lower incidence in the United Kingdom [112]. The American estimate predicted an annual incidence of 0.6/1000, whereas the British study predicted an incidence of 0.05/1000. A prospective study in the Canary Islands reported an incidence of 0.02 to 0.04/1000, with a mortality of approximately 70% [110]. The differences in the reported incidences of ARDS reflect in part the various criteria used for making

KEY WORDS
Lung: adult respiratory distress syndrome

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the diagnosis. In order to determine the true incidence of acute lung injury, it is important to standardize the definition and provide a more quantitative scoring system that includes both pulmonary and non-pulmonary organ function.

Therefore, we proposed an expanded definition [81] and this was endorsed by Dr Petty [90]. We will describe the three parts of the definition in some detail and we will also refer to the recent clinical and epidemiological studies that led to the formulation of this expanded definition.

Acute lung injury scoring system

The first part of the definition includes a semiquantitative method for scoring acute lung injury derived in part from criteria used by other investigators [38, 88]. The scoring involves a four-point system. First, the impairment of oxygenation is quantified by the ratio of the arterial oxygen tension to the fraction of inspired oxygen. Second, the chest radiograph is scored on a four-point system: if the chest radiograph is clear, then no points are assigned; one to four points are assigned for consolidation in the four lung zones. A radiologist is not needed to grade the film. Third, respiratory system compliance can be calculated (if the trachea is intubated) by dividing the tidal volume by the plateau airway pressure minus the positive end-expiratory pressure (PEEP). The fourth criterion reflects the PEEP. This is important for at least two reasons: PEEP obviously influences oxygenation, and the PEEP that is required provides some indication of the severity of respiratory failure. With this four-point scoring system, we classify acute lung injury as mild to moderate (0.1 to < 2.5) or severe (≥ 2.5) (table I) [81]. Using this scoring system in a prospective investigation of the sepsis syndrome, we found that severe lung injury or fully developed ARDS occurred in 25% of 40 patients who had sepsis; however, another 35% of the patients had only mild to moderate lung injury [113]. Thus this scoring system provides a broader view of the spectrum of acute lung injury that

TABLE I. *Components of the lung injury score*

	Value	Score
1. Chest radiograph score		
No alveolar consolidation	—	0
Alveolar consolidation in one quadrant	—	1
Alveolar consolidation in two quadrants	—	2
Alveolar consolidation in three quadrants	—	3
Alveolar consolidation in all four quadrants	—	4
2. Hypoxaemia score		
Pa_{O_2}/FI_{O_2}	≥ 300	0
Pa_{O_2}/FI_{O_2}	225–299	1
Pa_{O_2}/FI_{O_2}	175–224	2
Pa_{O_2}/FI_{O_2}	100–174	3
Pa_{O_2}/FI_{O_2}	< 100	4
3. Respiratory system compliance score (when ventilated)		
Compliance	≥ 80 ml/cm H_2O	0
Compliance	60–79 ml/cm H_2O	1
Compliance	40–59 ml/cm H_2O	2
Compliance	20–39 ml/cm H_2O	3
Compliance	≤ 19 ml/cm H_2O	4
4. PEEP score (when ventilated)		
PEEP	≤ 5 cm H_2O	0
PEEP	6–8 cm H_2O	1
PEEP	9–11 cm H_2O	2
PEEP	12–14 cm H_2O	3
PEEP	≥ 15 cm H_2O	4
The final value is obtained by dividing the aggregate sum by the number of components that were used:		
No lung injury		0
Mild-to-moderate lung injury		0 1–2.5
Severe lung injury (ARDS)		> 2.5

occurs after sepsis. It also provides a semi-quantitative method for following the physiological variables in patients with acute lung injury.

Clinical disorders associated with ARDS

The second part of the definition requires that the clinical disorder(s) associated with the development of ARDS be identified. Recent epidemiological studies of ARDS have been completed at a number of centres [38, 88]. These prospective studies identified sepsis syndrome and gastric aspiration as the two clinical disorders most commonly associated with ARDS (table II). Other clinical disorders associated with a risk for developing ARDS include shock of any aetiology, major trauma, multiple transfusions, severe acute pancreatitis, drug overdose, pneumonia and near drowning [96, 113]. The risk of developing ARDS increases with the number of clinical disorders that occur in the same patient. In addition, the time course for the development of ARDS after the onset of the clinical disorder has been examined. Overall, acute lung injury developed within 24 h in 80 % of patients at risk who ultimately developed ARDS. Subsequently, we carried out a prospective study of 40 patients with sepsis syndrome. We found that ARDS developed after sepsis in less than 6 h in many patients [113]. These findings have important therapeutic implications. It had been hoped that early treatment could be instituted to attenuate the severity of the acute lung injury. It may be difficult to achieve this objective, however, because the interval between the inciting clinical event and the development of acute respiratory failure is usually less than 24 h.

Sepsis is the most common clinical disorder associated with the development of ARDS: 20–40 % of patients with sepsis develop the syndrome. As injury to the pulmonary endothelium occurs early in experimental sepsis, we hypothesized that increased concentrations of von Willebrand factor (vWF) antigen, a product of both the systemic and pulmonary endothelium, might identify the patients with sepsis who would develop acute lung injury. We found that a plasma vWF-antigen concentration > 450 % of control had a sensitivity of 92 % and a specificity of 77 % for predicting acute lung injury. In addition, if a patient had non-pulmonary organ failure at the time of entry to the study (by definition, no lung injury could be present at this time) as well as a plasma vWF-antigen > 450 %, then there was an 80 % likelihood for the patient to develop lung injury and not survive [96].

The relationship between ARDS and sepsis has been investigated by other groups. In one study, if a patient had clinical evidence of infection and had positive blood cultures but the site of infection could not be identified before death, then the source of infection was usually found in the abdomen at postmortem [7]. In contrast, when patients had negative blood cultures with clinical sepsis, the postmortem examination showed that

TABLE II. *Incidence of ARDS following clinical risks (includes only those patients with a single risk event, not those with multiple risks). (Modified from data in [39] and [88])*

	Incidence of ARDS	
Clinical condition	Washington	Colorado
Sepsis		
Bacteraemia	—	9/239 (4 %)
Sepsis syndrome	5/13 (38 %)	—
Aspiration of gastric contents	7/23 (30 %)	16/45 (36 %)
Fracture	1/12 (8 %)	2/38 (5 %)
Multiple transfusions		
10 units/24 h	—	9/197 (5 %)
10 units/6 h	4/17 (24 %)	—
Cardiopulmonary bypass	—	4/237 (2 %)
Burn	—	2/87 (2 %)
Pneumonia in ICU	—	10/84 (12 %)
Disseminated intravascular coagulation	—	2/9 (22 %)
Pulmonary contusion	5/29 (17 %)	—
Near-drowning	2/3	—
Pancreatitis	1/1	—
Prolonged hypotension	0/1	—

TABLE III. *Direct causes of death in patients with ARDS and control subjects.* * *Three patients with sepsis and respiratory failure as contributing cause, one patient with respiratory failure as indirect cause.* † *Sepsis present as a contributory cause in all patients.* ‡ *Sepsis present as a contributory cause in one patient.* (*Reproduced, with permission, from* [79])

	ARDS group				Non-ARDS group			
	Early mortality ($n = 10$)		Late mortality ($n = 22$)		Early mortality ($n = 25$)		Late mortality ($n = 30$)	
Irreversible dysfunction (direct cause)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)
Sepsis	30	3	36	8	12	3	50	15
Cardiac	10	1	23	5*	4	1	3	1
Respiratory	10	1	18	4†	0	—	7	2‡
Central nervous system	30	3	18	4‡	52	13	33	10
Haematological status	0	—	4	1	12	3	3	1
Haemorrhagic shock	20	2	0	—	20	5	0	—
Hepatic	0	—	0	—	0	—	3	1

the origin of the infection was usually in the lung. Subsequently, Montgomery and co-workers [79] reported that both early and late mortality in patients with ARDS was related primarily to sepsis. The actual cause of death in the first 3 days after the onset of ARDS was respiratory failure in only 10 % of the patients. In fact, although the incidence of respiratory failure as a cause of death increased to 18 % in those who died after 3 days, most of these patients had a complicating pneumonia (table III). Another study reported that the overall survival rate was only 29 % in a group of 129 patients with ARDS [99]. Infection was much more common in non-survivors, and the lung and abdomen were again the most common sites of infection. Even when the patients received an appropriate course of antibiotics, the outcome was still poor (table IV).

TABLE IV. *Outcome determinants in ARDS.* ‡ *Includes patients with known site of infection only* † *Chi-square contingency analysis.* (*Adapted, with permission, from* [99])

		Survivors		
	Number	No.	(%)	†P
All study patients	129	37	29	
Infection				
Present	108	23	21	0.01
Absent	21	14	67	
Antibiotic therapy‡				
Adequate	69	20	29	ns
Inadequate	13	3	23	

Aspiration of gastric contents is another clinical disorder frequently associated with ARDS. To determine the extent of lung injury secondary to gastric aspiration, one study examined the prognostic value of gas exchange data in patients who had suffered an episode of gastric aspiration [16]. The authors measured arterial blood-gas tensions in 44 patients within 1 h after aspiration, and calculated the ratio of arterial oxygen tension measured to the alveolar oxygen tension delivered. If the ratio was 0.5 or less, mortality was 48 %; if the ratio was greater than 0.5, mortality was 14 % ($P < 0.05$). Thus by examining the initial oxygenation data, it was possible to assess the prognosis of patients with ARDS from gastric aspiration.

The adult respiratory distress syndrome develops also after major trauma. In some trauma patients, acute lung injury occurs in association with lung contusion or within the first 24 h of the trauma if severe hypotension occurs, emergency surgical treatment is required, or multiple transfusions are administered [88]. ARDS develops in other trauma patients when they develop sepsis syndrome several days after the initial trauma. In trauma victims with long bone fractures, the fat embolism syndrome and ARDS may develop [97]. Those that develop ARDS secondary to fat emboli have a much better prognosis than patients who develop ARDS following sepsis or immediately after major trauma, hypotension and surgical treatment. In ARDS patients with fat emboli, supportive treatment with mechanical ventilation should result in a greater than 90 % survival [97].

A number of other clinical disorders may be associated with the development of ARDS, including drug overdoses with aspirin, opioids, tricyclic antidepressants or barbiturates. Patients may develop acute lung injury from hypotension, concomitant gastric aspiration, or from direct lung injury from the ingested drug itself. Cardiopulmonary bypass is another important clinical condition associated with the development of acute lung injury. At our institution, the prognosis for ARDS following cardiopulmonary bypass is better than from other causes of acute lung injury [120]. In contrast, ARDS developing after bone marrow transplantation has a nearly 100% mortality [83].

Thus the clinical disorder or disorders that lead to the development of acute lung injury clearly influence the patient's prognosis for recovery. Therefore, the second part of the expanded definition requires that the associated clinical disorders should be specified, so that a more realistic assessment of the prognosis can be established at the onset of ARDS.

Non-pulmonary organ failure

The third part of the definition specifies the failure of organs other than the lung. The importance of non-pulmonary organ failure has been increasingly recognized in ARDS patients (fig. 1). Cardiovascular abnormalities were overlooked in the early descriptions of ARDS. In fact, an early requirement for the diagnosis of ARDS was the exclusion of cardiac disease. The literature suggests, however, that as many as 20% of patients with acute ARDS have concomitant cardiac disease [78, 129]. Because patients with acute and chronic cardiac failure have a higher risk of infection, it is reasonable to suppose that they may have a higher chance of developing ARDS and may have a worse prognosis because of their poor cardiac function. Furthermore, sepsis can cause a decrease in left and right ventricular function [18, 57, 85]. The decrease in ejection fraction tends to occur after the onset of sepsis and may resolve over a period of 7–10 days. These sepsis-induced cardiac abnormalities cannot be identified using a pulmonary arterial catheter; consequently, a radionuclide study is required to measure the decrease in ejection fraction [85]. Furthermore, stroke volume in this situation is not improved by increasing the intravascular volume [84].

Concomitant hepatic failure and ARDS are associated with an especially poor prognosis. Hepatic failure in the face of acute lung injury carries an almost 100% mortality [98]. In fact, any combination of three organs that have failed for more than 7 days carries a 98% mortality [61].

An example of the value of this new definition is provided by the study by Fowler and coworkers [39]. They reported that there were three variables at the onset of ARDS that correlated with a particularly poor outcome. Patients with ARDS had a mortality rate greater than 80% if the patient's initial pH remained less than 7.4

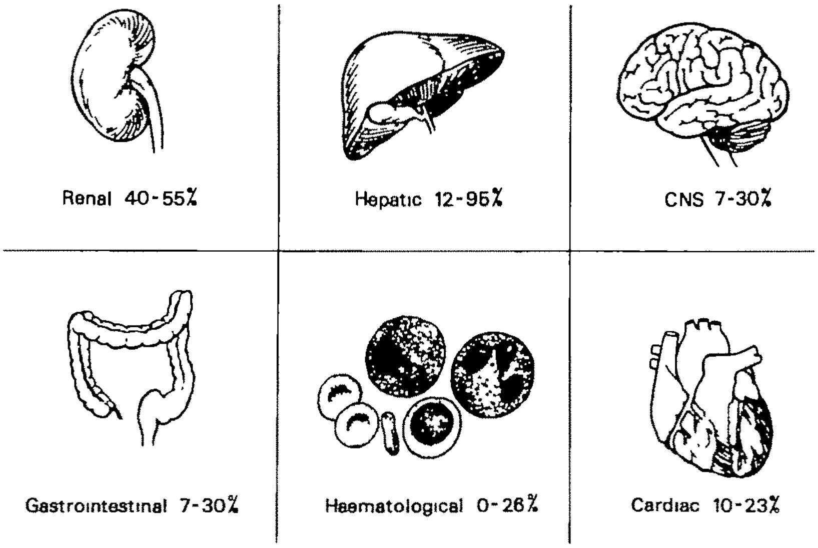

FIG. 1. Incidence of non-pulmonary organ failure in patients who have ARDS. Abnormalities are most consistently observed in the kidneys. However, hepatic dysfunction has also been reported in as many as 95% of patients with ARDS. (Reproduced, with permission, from [30].)

TABLE V. *Criteria for expanded definition of acute lung injury*

I. Severity of acute lung injury
  - Arterial oxygenation (Pa_{O_2}/FI_{O_2})
  - Chest radiograph
  - Static lung compliance
  - Level of positive end-expiratory pressure

II. Associated clinical disorder(s)
  - Sepsis (microbiology, anatomical site)
  - Aspiration (type)
  - Major trauma
  - Drug overdose
  - Cardiopulmonary bypass
  - Others (bone marrow transplant)

III. Systemic organ function
  - Acid–base status
  - Renal function
  - Haematological abnormalities
  - Hepatic function
  - Central nervous system function
  - Cardiovascular function

after the trachea was intubated and the lungs ventilated mechanically, if the initial serum concentration of bicarbonate was less than 20 mmol dl^{-1}, and if the initial concentration of blood urea nitrogen was greater than 23 mmol $litre^{-1}$ (65 mg dl^{-1}). The ARDS patients with these findings had an 80% mortality, compared with 40% mortality in the ARDS patients without these abnormalities. This is a good example of how systemic factors may influence outcome and why it is important to characterize a patient's pulmonary and non-pulmonary clinical status to develop a reliable prognostic system.

The three major categories in the expanded definition of ARDS [81] are summarized in table V. We believe that a more quantitative definition of pulmonary and non-pulmonary organ failure including the associated clinical disorders is critical for establishing the actual incidence of ARDS and for determining the prognosis for recovery [2, 6, 8].

PATHOPHYSIOLOGY OF ARDS

In the early phase of acute respiratory failure from acute lung injury, patients typically have severe alveolar oedema with large numbers of inflammatory cells, primarily neutrophils, in the air spaces and interstitium of the lung. Initially, the oedema fluid has a high concentration of protein (75–95% of plasma protein concentration) which is characteristic of an increased-permeability oedema [34]. Also, one group of investigators measured a rapid clearance of i.v. injected ^{131}I-albumin into the air spaces in patients with sepsis and acute lung injury [2]. Other methods for measuring lung microvascular permeability in ARDS patients have not yet been sufficiently reliable to be useful clinically [116]. Ultrastructural studies of the lungs from patients who died in the first 24 h after developing ARDS showed evidence of lung endothelial injury, presumably leading to the capillary leak and the increased-permeability pulmonary oedema [4] (fig. 2).

The early experimental studies of acute lung injury focused primarily on the injury to the pulmonary endothelium. However, morphological studies by Bachofen and Weibel in 1977 also showed considerable epithelial injury in patients dying of ARDS in the acute phase (fig. 2) [4]. Epithelial injury is now emerging as a very important component of the acute lung injury syndrome, partly because injury to the epithelium lowers the threshold for alveolar flooding and results in a substantial deterioration in gas exchange.

In fact, a recent clinical study in patients with ARDS has demonstrated that the presence or absence of normal alveolar epithelial function, as measured by sequential measurements of the concentration of protein in pulmonary oedema fluid, may be an important prognostic indicator in ARDS patients [120]. If patients can reabsorb excess alveolar oedema within the first 12 h after developing pulmonary oedema, alveolar epithelial function is reasonably intact. Patients in this category had an excellent chance for recovery from their acute respiratory failure and an excellent chance of survival overall. In contrast, patients who had no change in their pulmonary oedema fluid protein concentration in the first 12 h after the onset of mechanical ventilation (and therefore did not reabsorb any of the excess alveolar liquid), had a much higher mortality.

At first, airway abnormalities were not identified as an important feature of ARDS. Pulmonary function studies of ARDS survivors demonstrated that a large proportion of the patients who recovered from this disease had nearly normal pulmonary function. However, some patients with no prior history of smoking and no history of asthma did develop reactive airway disease after recovery from ARDS [52, 89]. Experimental studies have demonstrated that gram-negative

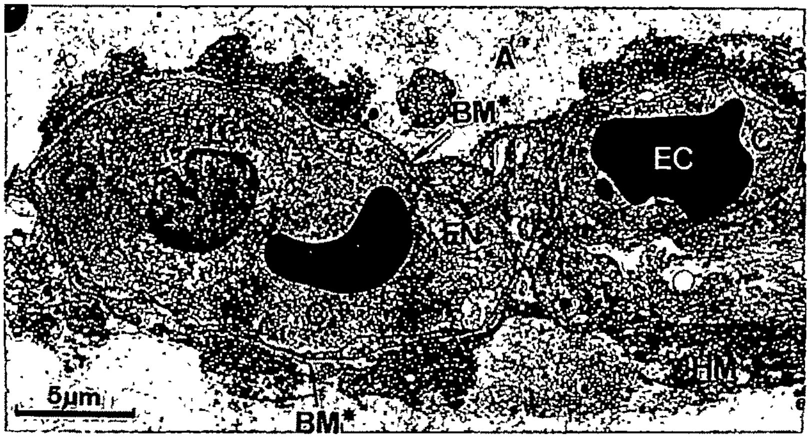

FIG. 2. Ultrastructure of a lung specimen, showing the alveolar septum with extensive epithelial destruction in a 19-yr-old woman who died after 4 days of fulminant capillary leakage as a result of septicaemia. Note the irregularly swollen and damaged endothelium. Also note that there is loss of the epithelial cell-lining in some areas where the basement membrane is exposed to the alveolar space. A = Alveolar space; BM = denuded basement membrane; C = capillary; EC = intravascular erythrocyte; EN = swollen endothelial cell; HM = hyaline membrane; LC = intravascular leukocyte. (Reproduced, with permission, from [5].)

endotoxaemia causes substantial airway constriction in sheep, which suggests that this mechanism of airway constriction may also occur during the patient's stay in hospital [102]. Bronchoconstriction is mediated by thromboxane and can be inhibited by cyclo-oxygenase block utilizing indomethacin [102]. Clinical studies have confirmed some of these experimental findings; airway resistance was increased in 50% of patients with ARDS in one hospital [122].

There is an equal incidence (approximately 40%) of pleural effusion in patients with hydrostatic or increased permeability pulmonary oedema [1, 119]. It has been established that approximately 20–25% of the excess lung water in acute pulmonary oedema that accumulates in the first few hours from increased permeability oedema drains into the pleural space and is cleared from the thoracic cavity by pleural lymphatics [117]. More lung oedema drains through the pleural space than through the lung lymphatics in experimental studies of respiratory distress syndrome in newborn lambs [12]. Thus the pleural space is an important route for the clearance of a significant fraction of pulmonary oedema fluid.

The interstitium of the lung becomes involved during the sub-acute phase of ARDS, approximately from day 5 to day 10 after lung injury. Some patients develop an accelerated fibrosing alveolitis. Ultrastructural studies have shown an impressive proliferation of alveolar type II epithelial cells, providing a new epithelial lining, apparently in response to injury of the type I alveolar epithelial cells in the acute phase. There is a pronounced increase in fibroblast and collagen formation in the interstitium (fig. 3) [71]. The mechanisms for these responses to the acute lung injury are not understood, but there is considerable interest in investigating the role of fibroblast and epithelial growth factors that may be released from alveolar macrophages and other cells in the lung.

Lung destruction occurs during the chronic phase of ARDS (10–14 days after the syndrome has developed). There is considerable evidence of lung destruction, emphysema and pulmonary vascular obliteration, in addition to areas of intense fibrosis. In this chronic phase, patients usually do not have as severe an oxygenation defect as they did in the acute phase when there was flooding of the air spaces with protein-rich oedema fluid. In the subacute and chronic phases, oxygenation usually improves and the requirements for PEEP may decline. The patients continue to have a large deadspace and require a very high minute ventilation, in excess of 15–20 litre, to maintain a normal arterial carbon dioxide tension. During this phase of the disease, there is still decreased lung compliance which may be secondary to the pulmonary fibrosis and insufficient surface active material.

Most patients do not die during the acute phase

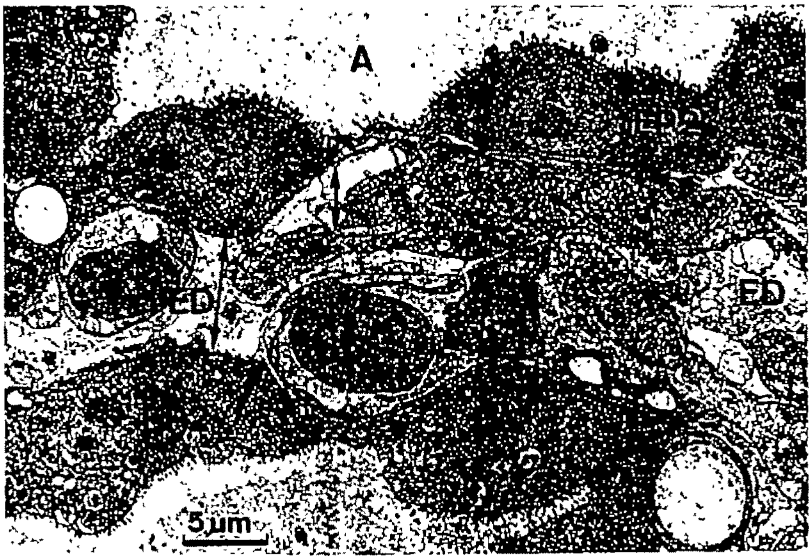

FIG. 3. Ultrastructure of a lung specimen from a patient about 1 week after near drowning, showing the histological features of the subacute stage of the adult respiratory distress syndrome. The septum is widened by interstitial oedema (ED), fibres and cells (double arrows) and an almost continuous layer of bulky epithelial cells resembling type II cells (EP2). The single bold arrows refer to areas of fused endothelial and epithelial basement membrane. The patient had persistent sepsis from an abdominal source for 1 week. (Reproduced, with permission, from [5].)

of lung injury [79]: they survive to develop the subacute and chronic phases of ARDS when secondary pulmonary and non-pulmonary infections determine the outcome. Nosocomial pneumonia is a common complicating problem in patients with ARDS, particularly during the subacute phase [23, 62]. The highest risk of infection appears to be during the first 6–10 days after the initiation of ventilation [62]. The mechanism for increased host susceptibility to infection is not well understood. Some studies of alveolar macrophage function have not shown any major alteration. One explanation may be that destruction of lung tissue results in an impairment of both blood supply and lymphatic drainage, and to the presence of cellular debris and plasma in the air spaces, predisposing these areas to bacterial growth. Since airway abnormalities have also been identified in some patients, it may be that mucociliary transport is impaired as well. This could result in the retention of secretions and a greater chance of developing pneumonia.

Recent studies of ARDS survivors have found that patients who were bacteraemic during their illness had a greater decrease in their diffusing capacity after they recovered. There was no correlation between pulmonary function and the duration of mechanical ventilation, the inspired concentration of oxygen or the period for which they required supplementary oxygen [89]. These results suggest that sepsis, not the required supportive care with supplementary oxygen, mechanical ventilation and PEEP, may be the primary factor influencing the magnitude of lung injury. However, another study showed a correlation between impaired post-ARDS pulmonary function and the maximal pulmonary arterial pressure, lung compliance and the maximal PEEP required during the patient's illness [41].

PATHOGENESIS OF ARDS

The co-existence of ARDS and sepsis is associated with a very poor prognosis. Consequently, this section will focus on the mechanisms of acute lung injury following endotoxaemia, bacteraemia and sepsis.

Infusions of live *Pseudomonas* bacteria into sheep that had lung lymph fistulae caused a marked increase in lung vascular permeability as reflected by an increase in protein-rich lung lymph flow [15]. E. coli endotoxin was shown to produce a similar pattern of lung endothelial injury in sheep, with an increase in protein-rich lung lymph flow within 2–4 h after the administration [76].

Other experiments have shown that both cellular and humoral factors are important in the pathogenesis of the early and late phases of endothelial injury after i.v. administration of endotoxin [102]. However, i.v. administration of endotoxin does not consistently cause pulmonary alveolar oedema, does not appear to cause alveolar epithelial injury [118] and does not fully replicate the adult respiratory distress syndrome. Nonetheless, endotoxin may play a role in ARDS, since detectable concentrations of endotoxin have been measured in patients who have ARDS [86]. Endotoxin studies in various animal models have been useful in examining the host response to injury and in identifying those resident lung cells and mediators which contribute to the acute lung injury seen in clinical septicaemia.

Neutrophils

There is abundant evidence to suggest that neutrophils play a role in the initial lung damage in patients who develop ARDS. Large numbers of neutrophils collect in the lung in the early phase of lung injury. In eight of 10 patients who subsequently developed ARDS there was peripheral leucopenia with a white blood cell count less than 4200 cells mm^{-3}. Of 30 patients with a similar risk of ARDS but who did not develop the syndrome, only four had the same level of leucopenia [106]. The implication was that peripheral leucopenia was associated with ARDS because neutrophils accumulated in the lung. Furthermore, some investigators have reported the development of ARDS in patients with severe neutropenia after chemotherapy [74, 93]. However, another group of investigators evaluated 116 patients with bacteraemia but did not find a relationship between leucopenia and the development of ARDS [35]. In the experimental studies of endotoxin-induced acute lung injury, peripheral neutropenia is a common finding, but neutropenia is not invariable or necessary for the development of ARDS after sepsis.

Some investigators have reported that, in patients with ARDS, neutrophils are in a functionally and metabolically activated state. Zimmerman and associates [127] reported that chemotactic responses of neutrophils in patients with ARDS were increased more than two-fold compared with neutrophils from control patients. Also, these investigators found an increase in generation of chemoluminescence by neutrophils from ARDS patients, suggesting that these granulocytes were likely to generate increased quantities of active oxygen metabolites [127, 128]. However, another group of investigators has reported more recently that neutrophils from the systemic and pulmonary arterial blood of patients with ARDS are not activated and did not respond more vigorously to chemotactic stimuli [91]. Therefore, the state of activation of the neutrophils in ARDS remains uncertain.

Neutrophil function can be divided into four phases: adherence, chemotaxis, phagocytosis and triggering of postphagocytic intracellular events designed to kill ingested micro-organisms. When neutrophils are incubated in plasma from septic shock patients, the neutrophils display increased adherence, implicating a soluble factor in the plasma [109]. Neutrophils from patients with bacteraemia have depressed chemotaxis [50] and it is important to recognize that depressed neutrophil chemotactic responses may be observed after the neutrophils have secreted their intracellular contents. In general, most investigators consider that these defects in phagocytosis occur because of the deficiencies of antibody, complement or the decrease in the number of neutrophils that occur in the patients that develop severe septicaemia [50].

One possible mechanism of neutrophil-dependent acute lung injury is that activated neutrophils sequester in the pulmonary circulation and release toxic oxygen products, proteolytic enzymes and products of the arachidonic cascade to injure the lung. Hallgren and associates [44] have reported that activated neutrophils and eosinophils are present in patients with ARDS, demonstrating increased circulating concentrations of lactoferrin and eosinophilic cationic protein, which are products of these activated cells. McGuire and colleagues [67] found increased proteolytic activity attributable to neutrophil elastase in lavage fluid taken from the lungs of patients with ARDS—another product of activated neutrophils. Another group of investigators has reported that the neutrophils in the air spaces of the lungs of ARDS patients have reduced oxidative metabolism compared with normal controls, suggesting that they may already have been activated [91].

In summary, there are probably both neutrophil-dependent and neutrophil-independent mechanisms responsible for lung injury. The issue of neutrophil-related lung injury will be explored further in the sections considering the role of oxidants and proteases in mediating tissue injury in the lung.

Platelets and coagulation abnormalities

Platelet abnormalities have been identified in patients with ARDS. In a study of septic patients at risk for developing ARDS, a platelet count less than 100000 mm^{-3} was associated with increased risk of ARDS. This study also demonstrated that there was considerable platelet sequestration in the reticuloendothelial system in such patients [35].

Patients at high risk for the development of ARDS but who do not develop the syndrome may also have coagulation and platelet abnormalities. In patients at risk for developing ARDS, 51% had thrombocytopenia, but did not progress to develop ARDS [106]. Another series [20] found that 50% of the patients at risk for developing ARDS had thrombocytopenia but did not develop the syndrome. Furthermore, several investigators have been unable to demonstrate platelet sequestration or disseminated intravascular coagulation in patients who have developed ARDS [31, 100]. It is clear that coagulation disorders, including thrombocytopenia and microthrombosis, can be associated with ARDS; however, these disorders are also found in patients with sepsis and major trauma who do not develop ARDS. While platelet and coagulation abnormalities may be associated with the pathogenesis of acute lung injury, these factors are not reliable, specific predictors for the development of ARDS.

Although it has been difficult to implicate platelets and the coagulation system in the initial phase of acute lung injury, recent investigations suggest an important role for local abnormalities in coagulation and fibrinolytic pathways that probably predispose to deposition of fibrin in the air spaces of the lung. These studies may account for the frequent finding of hyaline membranes and other precipitated proteins in the alveoli of patients with ARDS (fig. 4). Idell and colleagues [51] have recently reported that the bronchoalveolar lavage fluid from patients with ARDS contained inhibitors of the extrinsic coagulation pathway. They also found depressed fibrinolysis that was not the result of a local insufficiency of plasminogen, but rather of inhibition of both plasmin and plasminogen activator. These are important observations, because precipitation of protein in the air spaces of the lung may be one of the reasons why recovery from acute lung injury may be protracted. We have shown that soluble protein can be removed readily from the air space of the lung over a period of 6 days, as may occur under conditions of hydrostatic pulmonary oedema [9]. However, in the case of acute lung injury, protein precipitates in the air spaces and makes it more difficult for the cellular debris and protein to be removed. Clearance pathways in acute lung injury may depend on the phagocytosis of protein by macrophages and the slow removal of protein through lymphatics and capillaries.

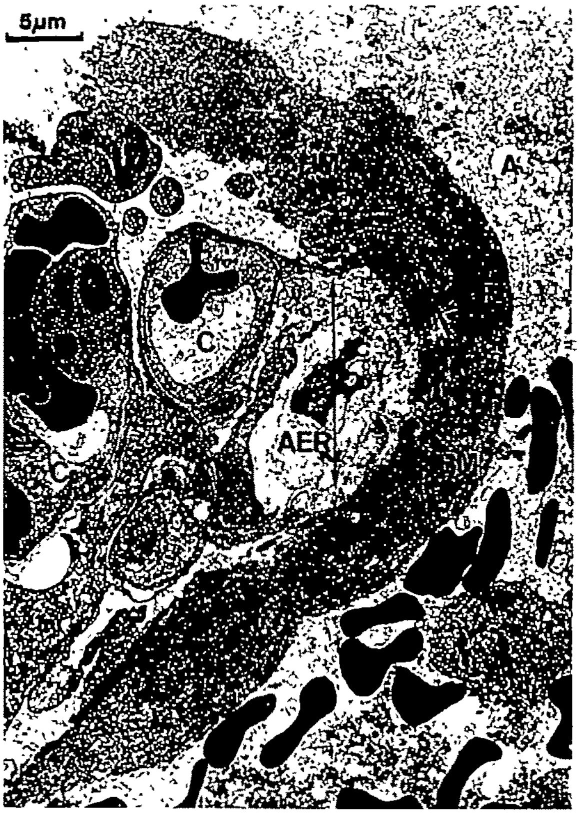

FIG. 4. Ultrastructure of a lung specimen from a 17-yr-old woman, who died of complications that included the adult respiratory distress syndrome 3 days after a traffic accident, showing an alveolar entrance ring (AER) covered by a hyaline membrane (HM) composed of condensed plasma protein and fibrin strands (F). Close contact of hyaline membrane to the epithelial basement membrane (BM) is restricted to an area of destroyed epithelial lamina. (Reproduced, with permission, from [5].)

Mononuclear cells

Considerable attention has recently been focused on the possible contribution of monocytes to lung injury because of the discovery that they are an important source of cytokines that may cause secondary lung injury. For example, monocytes release tumour necrosis factor, which reproduces much of the septic shock syndrome when given i.v. Monocytes also produce a variety of interleukins which may amplify the inflammatory response. Furthermore, alveolar macrophages secrete a variety of factors that recruit neutrophils to the air spaces of the lung and could potentially contribute to lung injury. In the past 5 years, an entirely new lung cell has been discovered, the intravascular lung macrophage, which may be important in modulating lung injury [111]. There are important species differences in the way intravascular macrophages respond to various stimuli, including their response to live bacterial organisms and endotoxin. A recent report indicates that intravascular macrophages do exist in the human lung and are estimated to exceed the total number of alveolar macrophages [27]. The release of intracelluar products of intravascular macrophages may contribute to the increase in the lung endothelial or epithelial permeability and contribute to lung injury in ARDS. Further progress must await success in isolating this cell in experimental studies and evaluating its contribution to lung injury under a variety of experimental conditions.

Endothelial cells

In vitro studies have suggested that endotoxin applied to endothelial cells directly affects endothelial monolayer permeability in the absence of leucocytes or monocytes [14, 47]. Structural studies of these endothelial monolayers show that the cells undergo contraction, become pyknotic and finally die [77]. These endothelial cells release significant amounts of prostacyclin [77]. Also, the permeability of the endothelial layers increases with the application of endotoxin [47, 77]. More *in vivo* studies are needed to test the mechanisms of injury suggested by these *in vitro* cell culture studies of the pulmonary endothelium.

Epithelial cells

Pathological studies have demonstrated that epithelial cell injury is prevalent in septic patients who die in the first 24–48 h after developing ARDS (fig. 2) The function of the alveolar epithelial barrier may be a very important indicator of the severity of acute lung injury in patients with acute ARDS and may be a prognostic indicator [120].

For many years, investigators have considered the possibility that some of the abnormalities in ARDS patients could be the result of decreased production of surfactant, production of an abnormal surface acting material, or inactivation of the surface acting material by the presence of protein-rich oedema in the air spaces of the lung during ARDS [45, 54]. There is still no conclusive evidence regarding the contribution of abnormalities in surfactant secretion or function as a cause of the physiological abnormalities. However, some of the data from studies in neonates using exogenous surfactant as treatment suggest a role for surfactant [54]. Clinical trials in the U.S.A. are beginning to treat patients with aerosolized surfactant in the hope that it may improve lung compliance, improve oxygenation and result in a shorter duration of mechanical ventilation.

The alveolar epithelium is responsible for the active removal of excess liquid from the air spaces of the lung by an active sodium transport system [69, 73]. In fact, both *in vitro* and *in vivo* studies have demonstrated that, in some species, the sodium transport system can be accelerated by treatment with beta-adrenergic agonists [10, 22]. Although it is intriguing to speculate that the clearance of alveolar liquid might be accelerated in patients with pulmonary oedema, more studies are needed to determine the relative rates of alveolar liquid clearance in man compared with other species and also to determine if epithelial cells in man are responsive to beta-adrenergic agonists.

Nevertheless, these data have provided important new information regarding epithelial cells and their critical role in both the recovery from acute lung injury and the removal of oedema fluid from the air spaces of the lung. The role of the alveolar epithelium in protein removal from the air spaces is unknown. Recent *in vivo* studies from our laboratory have demonstrated that the removal of soluble protein from the air spaces of the lung occurs relatively rapidly (1 % per hour) in unanaesthetized sheep; these studies may be more applicable to patients recovering from hydrostatic oedema than those recovering from ARDS, because much of the protein in the air spaces of patients with acute lung injury is insoluble. More information is needed to determine how insoluble protein is removed from the air spaces, and how epithelial injury changes these removal patterns.

Finally, the mechanism for injury to the alveolar epithelium must be identified. While endotoxin readily injures the lung endothelium, experimental data from our laboratory indicate that even high doses of endotoxin do not injure the epithelial barrier [118]. In contrast, live organisms do injure the alveolar epithelial barrier, causing an increase in permeability to protein [121]. The mechanism for this injury must be established, to permit a better understanding of the factors causing acute epithelial lung injury.

Complement system

Activation of the complement cascade has long been thought to be an important mechanism in the pathogenesis of acute lung injury. In particular, C3a and C5a are potent chemotactic factors for neutrophils, and both have been found in the bronchoalveolar lavage fluid obtained from patients with ARDS [94]. Several recent experimental studies have implicated complement as potentially important in the pathogenesis of lung injury. Specifically, a study in baboons demonstrated that anti-C5a antibody could attenuate the lethal effects of live *E. coli* organisms if given prophylactically [103]. Clinical studies measuring complement activation in plasma have found that concentrations of C5a are indeed increased in patients with sepsis, but do not predict the development of lung injury. However, in one study, concentrations of C5a correlated better with hypotension and metabolic acidosis than with the eventual development of acute lung injury [9]. Complement activation is clearly part of the pathophysiological process during sepsis leading to endothelial injury in both the systemic and pulmonary circulations, but complement activation alone may not be sufficient for the development of lung injury.

Prostaglandins/leukotrienes

The metabolites of arachidonic acid metabolism have been investigated extensively in a number of experimental models for their potential role in mediating acute lung injury. In experimental models where E. coli endotoxin is administered, cyclo-oxygenase products have been identified as mediating the initial pulmonary hypertension as well as the airway constriction that occurs after the infusion of endotoxin in sheep [102]. Conversely, treatment with indomethacin inhibits the pulmonary hypertension. The late phase response, when lung vascular permeability increases, is temporally associated with the elaboration of a variety of lipoxygenase mediators, not cyclo-oxygenase products. However, specific block of the lipoxygenase receptors does not clearly prevent the increase in permeability. Studies measuring mediators in bronchoalveolar lavage fluid and in pulmonary oedema fluid from ARDS patients have reported the presence of substantial quantities of leukotriene D4 [72]. This mediator has been shown to cause bronchoconstriction and vasoconstriction. The prostaglandins and leukotrienes are, therefore, undoubtedly involved in mediating some of the hypoxaemia associated with acute lung injury, but have not been clearly identified as major factors in the development of increased vascular permeability. Clinical studies in progress are evaluating the potential role of ibuprofen, a compound that inhibits prostaglandin metabolism and also has a stabilizing effect on neutrophils. The preliminary results of those studies indicate a mild improvement in oxygenation in some patients with ARDS [68].

Oxygen radicals

Oxidant-induced lung injury has emerged as a new focus for clinical and basic science investigations of acute lung injury. Consequently, many investigators have studied anti-oxidant and oxygen radical scavengers in an effort to attenuate acute lung injury [49]. Toxic oxygen products may be produced by a variety of mechanisms, including the activation of phagocytes and platelets. High inspired fractions of oxygen in patients in whom the trachea is intubated may be an additional source of toxic oxygen radicals. Finally, reperfusion of hypoxic tissue may well result in an additional oxidant burden.

The lung contains specific mechanisms for inactivation of oxygen radicals that are found both intracellularly and extracellularly (fig. 5). Within mitochondria, cytochrome oxidase reduces oxygen to water and acts as a sink for free radicals. Superoxide dismutase, catalase and glutathione peroxidase act together to minimize the concentrations of toxic oxygen products. Antioxidant activity is also found in vitamins A, E and C.

Specific treatments have been studied in attempts to attenuate oxidant lung injury in models of acute lung injury. It is well known that activation of neutrophils results in the generation of toxic oxygen products. It has also been shown that neutrophils are attracted to the lung in large numbers in many types of lung injury.

Using air emboli as a model of ARDS, Flick and colleagues [37] found that pretreatment of sheep with catalase attenuated transvascular liquid and protein flux, as measured by lung lymph flow, by approximately 50%. The same group has reported that administration of superoxide dismutase also decreased the effects of air embolism on lung injury [38]. Furthermore, Bernard and colleagues [8] reported that N-acetylcysteine attenuated the severity of acute lung injury in unanaesthetized sheep given E. coli endotoxin. N-acetylcysteine is an oxygen radical scavenger and also may have a direct effect on neutrophils.

An important consideration in any anti-oxidant enzyme therapy is the fact that these large molecules do not cross cellular membranes to a significant extent. Therefore, their effect might be limited in terms of modifying the intracellular environment. However, in the case of cellular injury with increased cellular membrane permeability, exogenous administration of these agents could be beneficial. Finally, one must consider the teleological basis of oxygen radical generation. A respiratory burst of neutrophils is an integral aspect of host defence against inspired micro-organisms. Since sepsis is the leading cause of death in ARDS, caution must be exercised in limiting those host defences.

Proteases

Proteolytic enzymes are important products of mononuclear cells and granulocytes that have the capacity to cause tissue injury. The tissue damage observed in the acute phase of ARDS with the subsequent fibrosis that occurs in the subacute and chronic phases highlights a possible role for proteases in the pathophysiology of acute lung injury. Enzymes such as elastase, plasminogen activator, plasmin and hyaluronidase can degrade the extracellular matrix, leading to increased vascular permeability through interruption of structural integrity. More importantly, degradation of the cell surface and basement membrane glycoproteins such as proteoheparin sulphate have been shown to disrupt the surface anionic charge and have been associated with increased microvascular permeability [104]. Trypsin, collagenase and elastase are all active in the chronic phase of ARDS when extensive fibrosis occurs. However, recent clinical studies have indicated that there is an excess of antiproteases present in the air spaces of patients with ARDS, suggesting that protease-related injury may not be a sufficient explanation for much of the lung injury [75].

Interestingly, on the basis of recent experimental and clinical work, there is a growing interest in a possible interaction between elastases and toxic oxygen radicals. In a recent review, Weiss [114] described an innovative mechanism whereby neutrophils could co-operatively use chlorinated oxygen to penetrate multiple antiproteinase barriers, thereby allowing elastase to attack susceptible tissues within the inflammatory focus (fig. 6). This hypothesis could be useful in explaining a synergistic interaction of both oxygen radicals and elastases in mediating acute lung injury. It has been shown in recent *in vitro* studies that neutrophils can generate and use both hypochlorous acid (HOCl) and N-chloramines to oxidize the surrounding alpha-1 proteinase inhibitor at a rate that permitted the elastase discharged from neutrophils to solubilize the

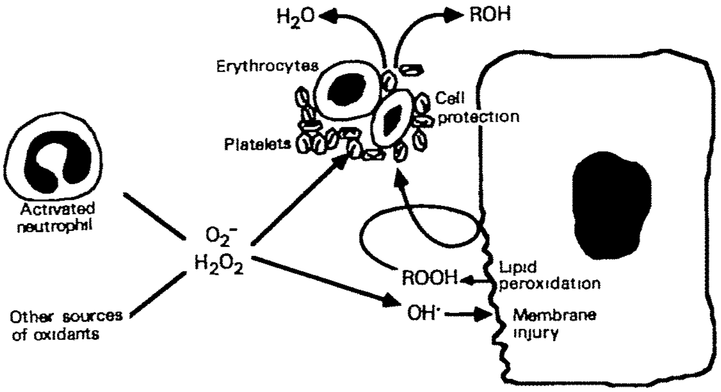

FIG. 5. A hypothetical antioxidant role for platelets and erythrocytes in the protection of endothelial cells from oxidant-induced injury. (Reproduced, with permission, from [49].)

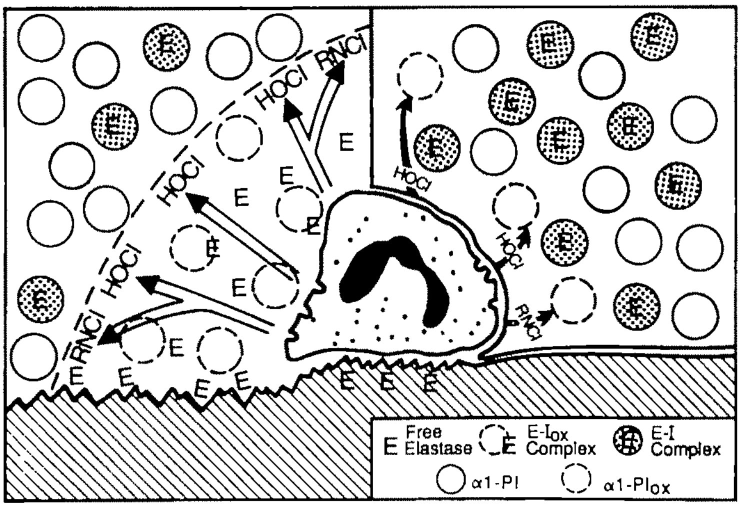

FIG. 6. The left half of the figure shows neutrophil oxidants creating a zone of oxidized α1-proteinase inhibitor (α1-PI) that allows released elastase (E) to attack and degrade tissues. Because oxidized α1-proteinase inhibitor (α1-PI_{ox}) can inhibit elastase only inefficiently, the enzyme may also be detected. The right half of the figure shows an alternative setting: only a small portion of the surrounding α1-proteinase inhibitor is oxidized, thus ensuring the efficient regulation of the released elastase. In either setting, proteolysis can occur to a limited degree subjacent to the neutrophil. (Reproduced, with permission, from [114].)

extracellular matrix [115]. Although neutrophils rapidly inactivate alpha-1 proteinase inhibitor *in vitro*, it should be recalled that elastase *in vivo* must still contend with both alpha-2 macroglobulin and secretory leucoproteinase inhibitor. Recent interesting studies indicate that both alpha-2 macroglobulin and secretory leucoproteinase inhibitor can be oxidatively inactivated by activated neutrophils. Thus all three components of the anti-elastase shield are potentially sensitive to oxidative attack. Only if neutrophils are prevented from generating HOCl can the antiproteinases remain active, in which case they are able to prevent tissue damage almost completely. Further *in vitro* and *in vivo* work will be needed to explore this hypothesis, but it may provide an important new advance in our understanding of the interaction of neutrophils, toxic oxygen radicals and proteases in mediating lung injury in patients with sepsis, gastric aspiration, or both.

Tumour necrosis factor and other cytokines

Tumour necrosis factor (TNF) is a peptide elaborated by mononuclear cells in response to endotoxin, interleukin-2 and several other mitogens. Tracy and colleagues [108] found that infusion of recombinant TNF into dogs reproduced the physiological changes normally seen with endotoxin, including hypotension, metabolic acidosis and death. TNF has been reported to be increased in some patients with sepsis [26]. Also, increased concentrations of TNF were found in children with meningococcaemia and severe infectious purpura [43]. Furthermore, Tracy and colleagues [107] attempted to attenuate septic shock by developing monoclonal antibodies to TNF which were used to immunize passively baboons which were then subsequently challenged with lethal doses of i.v. live *E. coli* organisms. This treatment was effective when the antibody was administered 2 h before the injection of live organisms, with complete protection from shock and organ failure, but the treatment was not effective if the antibody was given at the time the organisms were administered. TNF is clearly a potent, important mediator of septic shock, but its specific role in acute lung injury requires further evaluation.

Summary of pathogenesis

Much has been learned about the complex interaction of circulating and resident lung cells and how they may cause acute lung injury in man. The list of possible mediators released, both locally in the lung and systemically, has grown

TABLE VI. *Mechanisms for injury and repair in ARDS, 1990*

Circulating cells:	Platelets
	Neutrophils
	Monocytes
	? Lymphocytes
Resident lung cells:	Intravascular macrophages
	Alveolar macrophages
	Epithelial cells—Type II
	Fibroblasts
Possible mediators:	Complement system
	Prostaglandins
	Oxygen radicals
	Proteases
	Tumor necrosis factor
	Other cytokines

in the past decade. Further basic and clinical research will help to clarify how these factors interact as mechanisms for lung injury and repair in patients with ARDS (table VI).

CURRENT AND FUTURE MANAGEMENT STRATEGIES

Current and future therapy for ARDS may be separated into five separate categories.

Control of infection and its complications

The first and foremost issue to consider in the management of ARDS patients is the early diagnosis, treatment and prevention of infection. We have already reviewed the importance of sepsis as a cause of ARDS, in addition to its role in determining ultimate outcome after the acute phase of ARDS has subsided. It is important to reduce nosocomial infection by good handwashing, by wearing gloves, by removal of unnecessary intravascular or urinary catheters and prevention of skin ulcers, and to search for surgically treatable infections. If there is a positive blood culture and an unknown source for the bacteraemia, then surgical exploration of the abdomen is frequently helpful [7]. More recent suggestions for the prevention of nosocomial infections in critically ill patients include selective decontamination which involves the administration of *non*-absorbable antibiotics orally and topically to the oropharynx, in addition to the administration of i.v. antibiotics. Although mortality was not significantly affected, the incidence of late nosocomial pulmonary infections was decreased in the patients who received selective decontamination [63]. These patients did not have ARDS, so the applicability of this study to ARDS patients is unclear. However, a study of the administration of non-absorbable and i.v. antibiotics to baboons that had acute lung injury did result in a decrease in the number of organisms found in pulmonary specimens obtained at post-mortem [56]. Three regimens were found to be effective: topical polymixin and i.v. penicillin or gentamicin; topical gentamicin and i.v. penicillin or gentamicin; topical and i.v. gentamicin and penicillin. When antibiotics were not administered, polymicrobial pneumonia occurred in all animals [55]. The role of prophylactic antibiotics and decontamination regimens in patients who have ARDS is currently being investigated.

Immunotherapy is, perhaps, the most promising new therapeutic option for preventing and treating infection in patients with ARDS. Several studies have demonstrated that active and passive immunization using a rough mutant of the chemotype of *Salmonella minnesota* and the RC chemotype, J5 mutant, of *E. coli*, protected normal and granulocytopenic animals against challenges using heterologous Gram-negative bacteria or lipopolysaccharide (LPS) (endotoxin) [24, 66, 125]. In the clinical trials by Zeigler and Baumgartner, administration of antisera to *E. coli* J5 as treatment or prophylaxis to patients with Gram-negative bacteraemia resulted in a substantial decrease in mortality [6, 126].

However, more recent investigations using monoclonal IgG antibodies have produced inconsistent clinical benefit [123, 125]. McCabe and colleagues [65] attempted to explain these differences by comparing the protective activity of IgM and IgG immunoglobulin classes in post-immunization sera from rabbits and humans. They found that IgM induced protection similar to that observed for whole post-immunization sera, whereas post-immunization IgG alone afforded no greater protection than saline. These results were confirmed in a study by Calandra and colleagues [17] in which human IgG antibody to *E. coli* J5 was compared with a standard IgG preparation in the treatment of 71 patients with Gram-negative shock. The mortality was 50% in both groups.

Another study by McCabe further explored these issues by investigating the effects of a vaccine prepared from boiled, acetone-precipitated *Salmonella minnesota* R595, an Re chemotype mutant [28]. The vaccine was administered to 122 healthy volunteers and titres of antibody to the Re LPS, the basal core structure of endotoxin, increased in a dose-responsive fashion. Sera were harvested from these immunized volunteers and mice were passively immunized. Although passive immunization provided protection against gram-negative bacteria and endotoxin, there was no correlation between the degree of protection and the antibody titres to Re LPS, suggesting another immunodeterminant may be involved. Therefore, more research is needed to determine the protective factor in the sera raised against these non-virulent bacteria. The clinical role of immunotherapy will depend on isolating the key protective factors in serum and then administering them as early as possible to patients at high risk of Gram-negative infection or in the very early phase of Gram-negative sepsis.

Methods for improving gas exchange

There has been a continuing interest in new methods of mechanical ventilation for patients with severe respiratory failure from ARDS. However, such interest may be somewhat misguided, since many studies have shown that mortality in most ARDS patients can be attributed to uncontrolled infection and multi-organ failure, not primarily to respiratory failure [79].

In the extracorporeal membrane oxygenation (ECMO) study published in the early 1970s, a control group was treated with conventional mechanical ventilation while ECMO-treated patients received lower tidal volumes and had lower mean airway pressures [124]; the incidence of barotrauma and mortality was the same in the two groups. Subsequently, some investigators advocated PEEP, up to 40–50 cm H_2O, with the objective of reducing the intrapulmonary shunt fraction [59]. Although there was some initial enthusiasm that the increased PEEP improved survival in ARDS, the studies were uncontrolled. In fact, Nelson and colleagues [82] reported results of a randomized study of increased *vs* moderate PEEP and found no significant difference between the groups in terms of duration of mechanical ventilation or overall mortality. Finally, a prospective trial of the prophylactic use of 8 cm H_2O of PEEP in patients at high risk for developing ARDS showed no benefit in preventing acute lung injury [87]. There is no evidence that PEEP hastens the recovery from lung injury, prevents the development of lung injury or reduces extravascular lung water. Alveolar oedema is primarily absorbed by an active sodium transport pump which does not depend on the mode of ventilation or the airway pressure [53].

In the early 1980s, there was considerable interest in high frequency ventilation, partly because patients' lungs could be ventilated at lower peak airway pressures, which some investigators thought might cause less barotrauma and less ventilation-induced lung injury. However, subsequent work demonstrated that oxygenation with high frequency ventilation is strongly influenced by the mean airway pressure, especially in patients with ARDS [95]. Significant improvement in oxygenation could be achieved with high frequency jet ventilation (HFJV), but only if this was associated with an increase in mean airway pressure, which in turn often had a detrimental effect on venous return and cardiac output. Furthermore, a well designed prospective, randomized study of 309 patients showed that there was no significant difference in the total duration of intensive care or survival in patients managed with HFJV compared with conventional ventilation [19].

There has also been interest in other forms of ventilatory support, most notably the use of pressure-controlled, inverse-ratio ventilation. One retrospective study reported 31 patients with severe ARDS in whom conventional volume-controlled ventilation was ineffective [105]. The authors reported that use of pressure-controlled inverse-ratio ventilation was associated with a significant reduction of minute ventilation, peak airway pressure and PEEP, and a slight improvement in oxygenation. However, there was a significant increase in mean airway pressure, and pneumothoraces developed in six of the 31 patients treated with pressure-controlled, inverse-ratio ventilation. Overall mortality for the 31 patients with ARDS in this study was 77%. The study demonstrated the feasibility of this alternative method, but certainly did not indicate an improved outcome. In fact, until a prospective control trial is completed, clinicians should not use experimental modes of ventilation in patients with ARDS because they may in fact worsen outcome, particularly if mean airway pressure is markedly increased.

Some 15 years ago, a prospective study evaluated the possible value of ECMO as a means of resting the lungs and providing oxygenation and elimination of carbon dioxide for patients with severe ARDS [124]. That study showed no survival benefit using this technique. More recently, an uncontrolled Italian study reported favourable results with veno–veno extracorporeal membrane carbon dioxide removal in 47 patients with ARDS [40]. Although those results were encouraging, ECMO-treated patients cannot be compared with historical controls. Therefore, the National Institute of Health in the United States has sponsored a prospective study centred in the University of Utah in Salt Lake City to evaluate veno–veno ECMO as a treatment for ARDS. The results of that study are not yet complete, but to date the data show no difference between the control and ECMO-treated groups. Any new ventilation techniques must be subjected to the same prospective evaluation that would be required for a new drug [70].

Our current recommendation is that patients with acute respiratory failure in ARDS be ventilated with either assist-control ventilation or intermittent mandatory ventilation with judicious values of PEEP, usually between 5 and 18 cm H_2O. It seems reasonable to decrease the fractional inspired oxygen to less than 1.0 and if possible to 0.5. This is not always possible if the patient's respiratory function is very poor. There are very few experimental or clinical data to provide guidelines as to which patients will suffer from oxygen toxicity. Since most patients do not die from overwhelming respiratory failure, it seems reasonable to ventilate their lungs with an accepted conventional mode of ventilation with moderate PEEP.

Most studies show that surfactant replacement can improve lung compliance, although usually there is no definite effect in reducing the degree of inflammation or the degree of lung oedema [33, 48, 54]. Conceivably, surfactant replacement could improve lung compliance and allow patients' lungs to be ventilated at a smaller inspired oxygen concentration, with weaning from mechanical ventilation earlier than is currently possible. Surfactant has been shown to be inactivated by the presence of protein. This could be a problem with its administration during the active phase of ARDS [54]. Prospective randomized trials will be needed to demonstrate that surfactant replacement therapy really is useful in decreasing the duration of mechanical ventilation or decreasing mortality.

Limiting or decreasing pulmonary oedema

An important objective in treating patients with ARDS is to attempt to minimize the degree of pulmonary oedema. The primary mechanism for pulmonary oedema in patients with ARDS can be attributed to the increase in lung vascular and epithelial permeability. Nevertheless, modest increases in pulmonary vascular pressures, particularly left atrial pressure, will worsen the degree of pulmonary oedema [92]. One study did find that increasing amounts of lung oedema were associated with a higher mortality [32]. However, as another clinical study suggested, this result may reflect the fact that the more ill septic patients require administration of a greater volume of i.v. fluids to maintain their arterial pressure [101]. Thus increased extravascular lung water and increased body weight may simply reflect the increased vascular leak and extravascular accumulation of fluid in these patients. Standard clinical practice is to limit the increase in left atrial pressure as much as possible by judicious administration of fluids, to use diuretics if the patient is haemodynamically stable, and to avoid the infusion of large volumes of colloid that would increase left atrial pressure.

Improving systemic oxygen delivery

In many patients with ARDS, hypotension complicates the early phase of acute respiratory failure. In some patients, the hypotension may be attributed to hypovolaemia because of the combination of a systemic and pulmonary capillary leak syndrome as well as a PEEP-induced reduction of venous return. Therefore, modest volume expansion is the first treatment in these patients. Pre-existing heart disease is common and may require treatment with vasopressors and even afterload reduction with vasodilators [78, 129]. Co-existing sepsis may also affect cardiac function and overall circulatory responses [18, 25, 57, 85]. Dopamine can be used to support the arterial pressure and increase cardiac output. Even if invasive haemodynamic monitoring with pulmonary arterial catheterization is used, it is important for the clinician to rely on evidence of end-organ perfusion to evaluate the effects of therapy in terms of urine flow, arterial pH and mental status.

There has been considerable interest in the possibility that increasing oxygen delivery may help improve the survival rate among patients with ARDS, particularly those with sepsis. There is evidence that many patients with ARDS or sepsis also have occult tissue hypoxaemia as manifested by an increased oxygen consumption when oxygen delivery is increased [11]. Improved oxygen delivery in these patients may also improve organ perfusion and thereby reduce the incidence of multi-organ failure. However, no clinical studies have confirmed this hypothesis. In one study, cardiac output and oxygen consumption in patients with sepsis were improved by vasopressor therapy, but mortality was no better than in patients treated with i.v. fluids alone [42]. Further studies are required to evaluate the benefit of therapy directed at improving oxygen delivery in patients with ARDS.

Attenuation of pulmonary or systemic injury

The mainstay of current therapy is to reduce pulmonary injury by decreasing the inspired oxygen concentration to approximately 50% as soon as possible, with the judicious use of PEEP and optimal tidal volume. One study was able to show in an experimental model of lung injury that 50% oxygen did not produce additive toxicity [21]. In general, the clinician must balance the potentially toxic effects of increased concentrations of oxygen against increased PEEP which may cause barotrauma or decreased venous return. It seems reasonable to make every effort to wean the patient from 100% oxygen as soon as possible, partly because absorption atelectasis can be avoided if there is some nitrogen in the inspired gas mixture. Experimentally, most studies reporting severe oxygen toxicity have used 100% oxygen. We recommend that patients' $F\text{I}_{O_2}$ be reduced to 0.9 as soon as possible. Further reductions in the concentration of oxygen should be a major goal, providing that PEEP greater than 15–18 cm H_2O is not required. In addition, the acceptable Pa_{O_2} depends somewhat on the patient's underlying medical problems. If the patient has coronary artery disease, a Pa_{O_2} between 10 and 12 kPa is reasonable, whereas if the patient has no evidence of heart disease then Pa_{O_2} between 8 and 9 kPa should be adequate, as oxygen saturation will be greater than 90% in this range.

A number of drugs have been evaluated in the hope that one or more would be useful as treatment for reducing the severity of lung injury. Corticosteroids, oxygen radical scavengers, prostaglandin inhibitors, anti-TNF antibodies and other anti-inflammatory agents have been shown to reduce the severity of early lung injury. However, in a number of these studies, the drug was administered as prevention and not as a treatment. Even in patients to whom treatment was administered *after* the onset of lung injury, the time interval between the administration of treatment and the onset of lung injury was relatively brief.

Although corticosteroids have been shown to reduce lung injury experimentally, a number of clinical studies have now shown that there is no benefit to most patients with ARDS [64]. However, Webster and colleagues found a benefit in their U.K. series [112]. Corticosteroids have not been shown to be beneficial in terms of morbidity or mortality in patients with sepsis [13]. In addition, there have been some recent studies using pentoxifylline, an anti-inflammatory agent,

TABLE VII. *Summary of current and future treatment of ARDS*

	Current	Future
1.	Infection: prevention, early diagnosis and treatment	Immunotherapy Selective decontamination
2.	Improve gas exchange, reduce barotrauma: PEEP	Improved ventilatory modes Surfactant therapy
3.	Limit or decrease pulmonary oedema. diuretics, lowest left atrial pressure	Beta-adrenergic agonists
4.	Improve tissue oxygen delivery: volume, vasopressors	Vasodilators
5.	Attenuate pulmonary or systemic injury: decrease fraction of inspired oxygen	ECMO (venous bypass) Oxygen radical scavengers Anti-TNF antibodies Pentoxifylline

to attenuate endothelial leak in acute lung injury [46, 116]. However, pentoxifylline is a vasodilator and some of its effect on endothelial leak may depend on this property. Conceivably, pentoxyfylline, prostaglandin inhibitors or anti-oxidant therapy may be useful in limiting the degree of endothelial permeability in acute lung injury. Also, there has been some enthusiasm for the treatment of-patients with antibodies specific to circulating mediators of sepsis and lung injury. As mentioned, one experimental study showed that anti-TNF antibodies could prevent the occurrence of shock and death in baboons given live *E. coli* organisms [107]. However, for this treatment to be effective, it was necessary to administer the antibody 2 h before the administration of live *E. coli* organisms! There has been some interest also in monoclonal antibodies to the adherence-promoting leucocyte glycoprotein, CD18, as a method for reducing systemic organ injury. Lung injury was not attenuated, but functions of other organs were improved [29]. Treatment with this type of therapy might also make the host significantly more susceptible to infection. Many more experimental and clinical studies will be needed if the safety and efficacy of these new therapeutic approaches are to be confirmed.

Finally, recent work has suggested the involvement of a variety of polypeptide growth factors in the fibrosing alveolitis of ARDS [58]. Conceivably, specific therapy to inhibit unrestrained fibroblast proliferation after the onset of acute lung injury could attenuate the severity of the subacute to chronic phases of ARDS. However, development of this type of therapy and its application to a clinical setting will require much more basic research and then careful testing in clinical studies.

A summary of currently accepted modes of therapy for ARDS is provided in table VII. Possible future approaches are also listed. A realistic evaluation of any new treatment regimen will depend on a careful assessment of the extent of lung injury (table I), the associated clinical disorders and the extent of non-pulmonary organ failure (table V). As mortality is greatest in patients with sepsis-induced ARDS, this is the group of patients that could benefit most from new treatment regimens—particularly advances in immunotherapy which might improve host defences and attenuate systemic and pulmonary injury.

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HIGH FREQUENCY VENTILATION: PAST, PRESENT AND FUTURE?

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High frequency ventilation of the lungs has become the most popular subject for research papers and review articles in the anaesthetic literature, with well over 1000 titles published so far. Why should this be so? The question has many answers. To the clinician, high frequency ventilation offers the prospect of improved patient care and perhaps reduced morbidity and mortality in the operating theatre and in critical care. To the respiratory physiologist is poses what at first sight appears to be a fundamental challenge to the accepted laws of respiratory mechanics, with adequate gaseous exchange resulting from the use of a tidal volume equal to, or even less than, the apparent deadspace volume. To the physicist it is a phenomenon which demands investigation and explanation within the framework of the laws of thermodynamics, acoustics and fluidics. Even research biologists believe that investigation of this subject may hold the key to understanding the gaseous exchange mechanisms in the lungs of lower animals and birds [47].

The most fundamental difference between high frequency ventilation (HFV) and conventional intermittent positive pressure ventilation (IPPV) is that with HFV the tidal volume (V_T) required is approximately 1–3 ml kg/body weight, compared with 6–10 ml with IPPV. The increase in ventilation rate to frequencies of 60 b.p.m. or more in HFV is obviously mandatory if even comparable minute volume ventilation is to result. What is fascinating is that, if V_T is reduced to the apparent physiological deadspace volume, in theory even an infinite increase in frequency could not restore adequate alveolar ventilation. The obvious solution to this paradox must be that the physiological deadspace volume is smaller than the generally accepted value of 2 ml kg^{-1}, at least in some situations.

KEY WORDS
Ventilation: jet, HFJV

The concept that pulmonary gas exchange could be maintained with such small tidal volumes is not new. As long ago as 1915, Henderson, Chillingworth and Whitney [24] speculated that "there may easily be gaseous exchange sufficient to support life even when the tidal volume is considerably less than the dead space". A series of simple but elegant experiments reinforced this view. They showed that tobacco smoke blown into a tube formed a long thin central plume, and that "the quicker the puff, the thinner and sharper the spike of smoke". When the puff of smoke stopped,"the spike breaks instantly everywhere and the tube is seen to be filled from side to side with a mixture of smoke and air".

More than half a century was to pass before the implications of these findings was appreciated. In 1969, Oberg and Sjostrand published details of a new ventilatory technique (now termed High Frequency Positive Pressure Ventilation) which operated at 60–100 c.p.m. with tidal volumes close to physiological deadspace volumes [39]. Shortly after, Lunkenheimer and colleagues noted that apnoea resulted from the application of transtracheal pressure vibrations in dogs, and that adequate gaseous exchange could be maintained for prolonged periods without any obvious bulk flow of gas [31]. This was the first reported use of what is now termed High Frequency Oscillation. Again, the technique appeared to go almost unnoticed until 1980, when Bohn and colleagues confirmed the adequacy of gaseous exchange, and showed that this could be maintained almost indefinitely [5].

Simultaneously, in the U.S.A., Klain and Smith [26] used a modified form of Sanders' injector [46] to deliver high frequency gas pulses to the airway.

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This was the birth of High Frequency Jet Ventilation.

CLASSIFICATION OF HFV TECHNIQUES

The historical background above provides a useful method for classifying HFV techniques:

High Frequency Positive Pressure Ventilation. Tidal volume is delivered via a normal sized tracheal tube with inspiration being the only active part of the ventilatory cycle (i.e. expiration achieved by passive lung recoil). Frequencies are usually in the range 60–120 c.p.m. (1–2 Hz).

High Frequency Jet Ventilation. Tidal volume is delivered via a narrow cannula or injector resulting in a jet of high velocity gas, normally at frequencies of 60–600 c.p.m. (1–10 Hz).

High Frequency Oscillation. Tidal volume is delivered via normal sized tracheal tubes and both inspiration and expiration are active and of approximately equal power, such as would occur with an oscillating piston or loudspeaker-based ventilator. Frequencies range from 2 Hz to more than 100 Hz (6000 c.p.m.).

High Frequency Positive Pressure Ventilation (HFPPV)

This technique uses either modified conventional IPPV ventilators or purpose-designed low compliance systems to deliver tidal volumes of 2–4 ml kg^{-1} at respiratory frequencies of 1–2 Hz [39]. Systems have been developed also which incorporate expiratory valves, permitting a greater degree of controlled volume ventilation [49]. While in many cases a high pressure gas injector may be used within the ventilator, it is the nature of the gas pulse delivered to the patient which determines the classification. A jet injector sited some distance from the patient, but connected by a length of relatively large-bore tubing to the tracheal tube results in a pulse of gas which has a large surface area wavefront and a low velocity. In essence, the gas pulse acts as a piston within the tracheal tube. Any high frequency jet ventilator can therefore be used to provide HFPPV, but the converse is not true.

HFPPV has become popular in some centres, notably in Scandinavia, for endoscopy, and to a lesser extent for airways surgery [49]. This enthusiasm does not seem to be reflected worldwide, however, where HFPPV has made little clinical impact.

High Frequency Jet Ventilation (HFJV)

In HFJV, a burst of gas is delivered to the airway at high velocity via a relatively narrow cannula. Gas velocities in some systems may be as great as 300 m s^{-1} (Mach 0.9). This pulse of gas represents the tidal volume, and is the only active phase of the ventilatory cycle, as expiration relies on passive recoil.

The entrainment of gas from a second, low pressure circuit is a common but not invariable feature [10]. However, Smith, Scott and Fischer [55] took the view that, in the clinical setting it would be difficult to control the final tidal volume, the inspired gas tensions and the degree of humidification required in such a system, because of unpredictable and varying patient compliance. In a system of this type, any increase in patient compliance reduces the entrained volume, leading to a reduction in tidal volume and alteration of the inspired gas tensions unless both "jet gas" and entrained gas have come from a common source [3]. The popularity of entrainment systems derives from the fact that, in most cases, only the low pressure gas stream can be humidified. As humidification is a prerequisite of HFJV of more than a few minutes duration, entrainment becomes an essential, if inefficient, feature. Only those systems in which the main jet gas is humidified can be used for prolonged periods if the hazards of airway damage, ciliary destruction and retention of secretions are to be avoided [51].

In essence, HFJV behaves as a Sanders injector [46] operated at a high frequency and small volume. As such, the important variables in clinical practice are the driving pressure, frequency and the inspiratory time (which determines the inspiratory to expiratory (I:E) ratio). The minute volume delivered depends only on the driving pressure and the I:E ratio, thus the ventilator will behave as a minute volume divider, with progressive reduction of tidal volume as frequency is increased. An understanding of this point is crucial to the clinical use of HFJV as simply increasing the ventilation frequency will lead to a reduction in alveolar minute volume and hypercapnia.

The position of the jet injector within the airway has varied enormously from one centre to another [2, 9, 19]. The most common arrangement is to site the injector at the proximal end of the tube, the low position (at the distal end of the tube) having fallen largely into disuse. It had been thought by some workers that this low position would enable smaller tidal volumes to be used by bypassing part of the system deadspace. Unfortunately, the efficiency of any jet injector depends upon the driving pressure used, the jet cannula to tracheal tube radius ratio, and the geometry of the injector itself [3]. Any advantage gained by using the low position is immediately offset by a reduction in the efficiency with which the jet controls gas flows within the tracheal tube. In addition, with the low position, even minor degrees of movement of the tracheal tube can lead to predominantly unilateral lung ventilation [19]. Fears have also been expressed regarding the possibility of direct mucosal damage in the region of the carina as a result of the high velocity jet impinging on this area, and because of thermal injury resulting from gas cooling as a consequence of the Joule–Kelvin effect as it issues from the jet injector [53].

Clinically, HFJV has been used in a wide variety of patients in the Adult Intensive Care Unit [55] and in the operating theatre for a wide variety of procedures including endoscopy and otorhinolaryngology, and thoracic, abdominal and neurosurgical techniques [19]. One unique attribute of HFJV is its ability to deliver adequate ventilation via narrow cannulae inserted by either the tracheal or transtracheal route (including the cricothyroid membrane), for both elective and emergency ventilation [10, 55].

High Frequency Oscillation (HFO)

In HFO the ventilator is usually a reciprocating pump of the piston variety, although some have been based on a loudspeaker system driven by an electronic oscillator. Both systems generate a sinusoidal respiratory flow pattern. From this, it follows that the I:E ratio is usually fixed at 1:1, although variable-ratio pumps have recently been described [19]. The pump is used to produce a reciprocating flow in the airways, whilst an auxillary gas flow, usually termed the bias flow, is used to clear the extracted carbon dioxide and to provide fresh gases to the system. These systems behave as a T-piece circuit, and the efficiency of carbon dioxide removal is, at least in part, a function of the magnitude of the bias flow. The sinusoidal flow pattern is relatively easy to analyse mathematically, and it is not surprising that HFO has been used extensively in bench testing and animal experimentation [37].

While at first sight this might seem reasonable, it may in fact be quite inappropriate to use sine wave generators in fundamental research. In the analysis of linear systems which contain resistive, capacitative and inertial elements, the use of a sine wave input yields relatively little information as regards the mode of action of each element, and even less as regards the interactions between elements. If the input is a sine wave, the output at any point within the system can only be a sine wave. Whilst it is true that there may be differences in amplitude and phase shift between differing points in the system, these are the only signal modifications possible. Far more information may be derived by studying the effects of the network (i.e. the respiratory tract) on other types of waveform. In this respect, it might be more appropriate to study the behaviour of square and triangular respiratory waveforms.

Despite the extensive non-clinical use of HFO, there has been relatively little enthusiasm for its use in the clinical setting, and there is certainly no evidence to show any clinical superiority of HFO over other modes of ventilation.

Functional classification

Just as there is little standardization of HFV equipment, there is little agreement as regards the nomenclature in HFV studies. Froese and Bryan [19] have advocated the introduction of two broad functional classifications, namely high frequency ventilation-active, "HFV-A", and high frequency ventilation-passive, "HFV-P". HFV-A refers to those systems in which expiration is actively assisted, whilst HFV-P denotes entirely passive expiration. Each HFV mode can then be classified further according to the mode of action of the particular ventilator; thus classical HFJV systems would be HFJV-P, while those with a second jet activated to assist expiration would be HFJV-A. The appending of the suffixes -A or -P to other systems follows the same rule. While in the short term this might appear to confuse the situation further, it is only through a clear separation of ventilatory modes that the data derived by different workers can be analysed and interpreted. All forms of HFV are not the same and the general introduction of such a system of classification is long overdue.

MECHANISMS OF ACTION OF HIGH FREQUENCY VENTILATION

In the past 5 or 6 years, the plethora of papers concerned with the mechanisms of gaseous exchange during HFV have served only to confuse rather than clarify the situation. This is to be regretted, as many clinicians have become more, rather than less, confused about HFV. There are, of course, exceptions to any rule and there are several excellent reviews which can be recommended to the reader [11, 13, 19].

There are a number of mechanisms proposed to explain the apparent paradox of gaseous exchange in HFV.

Direct alveolar ventilation. There is no doubt that tidal volumes less than 2 ml kg^{-1} will still produce direct alveolar ventilation of alveoli with short path lengths—that is, the more centrally situated alveoli. Even tidal volumes of 1 ml kg^{-1} show this effect which, it should be noted, occurs even in normal spontaneous ventilation [6, 24]. In HFPPV and HFJV this mechanism probably accounts for 50–75 % of gaseous exchange.

Asymmetric velocity profiles. The fluid dynamics within the conducting airways are complex, and are markedly different during inspiration and expiration. These effects are particularly marked in the region of bronchial bifurcations. The final result of these effects is an increase in convective transport of respiratory gases which should, in theory, favour oxygen delivery more than carbon dioxide elimination [23].

Taylor dispersion [56]. This is in effect a formal statement of the observations made by Henderson, Chillingworth and Whitney, mentioned earlier [24]. It proposes a mixture of convective transport along the airways, with diffusion occurring radially within each major bronchus. The exact contribution of this effect to overall gas transport is difficult to assess, but while it may play a minor role in HFJV and HFO, it is probably insignificant in HFPPV.

Pendeluft [1, 18]. As the frequency of ventilation increases, the distribution of the tidal volume becomes increasingly dependent upon segmental, rather than overall time constants. This leads to asynchronous filling and emptying of adjacent lung units with "slow" units filling from "fast" units. This leads to intrapulmonary gas shunts or pendeluft, which results in more uniform gas mixing. The asynchronous movement of the lung in this way has been nicknamed "Disco Lung" [29].

Cardiogenic mixing [50]. The cardiac impulse can produce small pressure waves within the thorax, which produces some degree of gas movement and mixing. The contribution of this effect to overall ventilatory exchange is minimal.

Accelerated diffusion. In all forms of ventilation, diffusion is ultimately responsible for conveying gases between the conducting airway and the alveolar units. The claim that this component is somehow accelerated in HFV is unsupported. This is hardly surprising, because the factor which primarily determines the rate of molecular diffusion of any gas of given density is the absolute temperature. Unless the temperature increases, there can be no acceleration of diffusion.

Acoustic resonance. A completely new approach to the understanding of HFV has been proposed by Lin and Smith [30]. In their analysis, the ventilator is modelled as an acoustic source—that is, a source of pressure waves which behave according to the laws of acoustics and thermodynamics. These pressure changes are conveyed to the patient who thus becomes an acoustic load—that is, a dissipator of acoustic energy. This analysis has two parts, namely the low frequency (0–50 Hz) and high frequency (50–20000 Hz) domains.

The low frequency acoustic model

Conventional lung modelling treats the lung as having two basic determinants of gas flow, namely resistance and compliance (or capacitance). There is a third element, inertance, which is usually ignored. This is reasonable at ventilatory frequencies less than 30–40 b.p.m., when its contribution is small, but as frequency increases the contribution of inertance to overall pulmonary mechanics becomes much more important. Ultimately, the principal determinant of tidal volume distribution will be inertance. Regional variations in airway resistance and segmental compliance will thus have a decreasing influence in gas distribution. This has been confirmed by several groups of workers in both experimental and clinical fields [27, 35, 42].

The inclusion of inertance in this model has another important consequence. Because the respiratory system can now be regarded as a three-component model (namely resistance, capacitance and inertance) it behaves as a simple mechanical oscillator driven by a suitable exciting (i.e. ventilation) frequency. Using a standard formula and derived values for the parameters, it can be calculated that this frequency should be about 4–7 Hz in the adult human, 3–10 Hz in pigs and 4–8 Hz in dogs. The author and other workers have produced evidence to support these predictions [22, 43, 54]. It is interesting to note that, in dogs exposed to thermal stress, panting occurs at the resonant frequency of the animal's respiratory system [34].

The implications of resonance are profound. In any resonant system there is an interconversion of potential and kinetic energy. In the case of the respiratory system, potential energy is represented by the intrapulmonary gas pressure, while kinetic energy is represented by movement of gas and the respiratory system as a whole. If the lung were to be ventilated at its resonant frequency, maximal gas movement would occur for minimal airway pressure swings—a feature of obvious clinical interest. In the case of the panting dog, resonance means that minimal energy expenditure is required to produce maximal gas movement. Such optimization of gas dynamics is obviously attractive to the clinician, but there is a drawback. If the ventilation rate matches the resonant frequency, an airway pressure swing of normal amplitude could result in dangerously maximized intrapulmonary pressures. This effect has been observed in experimental animals, with fatal results [54]. It would seem prudent that, unless the resonant frequency of any particular patient is known accurately, ventilation rates should be restricted to a maximum of about 3 Hz (180 b.p.m.).

The possible effects of resonance on other organ systems are as yet entirely speculative, but they could at best be unpleasant for the patient if not actually harmful, at least in the case of large amplitude movements [14, 21, 36]. This low frequency model does not mean that conventional respiratory physiology is wrong. In much the same way that Newtonian mechanics hold good for objects at low velocities, conventional pulmonary mechanics apply at low ventilation rates.

The high frequency acoustic model

The pulse of gas injected through the cannula in HFJV systems produces considerable acoustic output in the audio frequency range of 20 Hz–20 kHz (i.e. it produces noise). The exact frequency spectrum generated depends upon the radius of the cannula and driving pressure used [52]. The scatter of resonant frequencies of the trachea and bronchi extends from about 500 Hz for the trachea to 20 kHz for smaller bronchi [30]. Lin and Smith concluded that it was likely that the audio frequency output of the cannula would induce resonance within each bronchus. It has long been known that resonance within a tube results in considerable turbulence within the contained gas [41]. Such turbulence can increase considerably the rate of mixing of carbon dioxide and air [52]. If this were to occur in the airways there could be a considerable increase in the rate of carbon dioxide removal and oxygen delivery. A study has supported this view, and may be the first plausible explanation of "accelerated diffusion" [55]. It must be noted, however, that this is a convective mechanism, not a diffusive effect.

HIGH FREQUENCY VENTILATION: CLINICAL CONSIDERATIONS

Control of breathing

There is considerable confusion in the literature as to whether HFV *per se* causes inhibition of spontaneous ventilation [8, 16, 17, 28, 32, 57]. Such an effect is seen in experimental animals and in human infants, but not in adult humans, at least as regards HFJV. A study has confirmed that, providing arterial carbon dioxide tension is not depressed, spontaneous ventilation does occur during HFJV [55]. This allows HFJV to be used as a form of mandatory minute volume ventilation in the weaning of patients. It is not yet clear if this is the case with other HFV modes.

Gas trapping

This is a problem common to all types of ventilation, but assumes increasing importance as the ventilatory frequency increases. The effect is particularly marked if the expiratory time is reduced to less than 250 ms. The shorter the expiratory period and the greater the respiratory time constants, the lower the frequency at which gas trapping becomes a problem [45]. A modest degree of gas trapping is not always undesirable, and the term "auto-PEEP" may give a more balanced view of this effect [4]. It should be noted that the proximal airway pressure is a poor indicator of true intrathoracic pressure during HFV, and oesophageal pressure may be a better index for clinical use [55].

It has been argued that gas trapping is less likely to occur in HFO systems in which expiration is assisted [19]. If the conducting airways were rigid structures this might be true, but in reality the airways are more likely to close as a result of the negative pressure phase, with increased gas trapping and reduction of ventilatory efficiency [12].

Humidification during HFV

Humidification of the fresh gas flow during HFPPV and HFO is not a problem. Unfortunately, whilst HFJV is undoubtedly the most useful clinical mode of HFV, it is also the most difficult to humidify [51]. The need for good humidification in HFJV is paramount. The fresh gas flows required in HFJV when used clinically can easily exceed 30 litre min^{-1}. Even 75% humidification would mean that the drying effect on the respiratory tract would be the equivalent of 7.5 litre of dry gas each minute. Early attempts to overcome this problem used a conventionally humidified low pressure gas stream which was entrained by the jet injector. The final gas mixture would at best be only 75% saturated and, in patients with reduced pulmonary compliance, this figure could decrease to as little as 10%. Clearly, those systems that rely on entrainment cannot be used clinically for more than the briefest period of HFV [38].

Cooling effects of HFV

Excessive cooling of the patient has entered the folklore of HFV as a practical problem. There is no documented evidence for such a claim, provided that adequate humidification is provided. The gas flows used in HFV may be high, but the thermal capacity of gases is very low. In contrast, the latent heat of vaporization of water is considerable. A few quick calculations reveal the relative importance of humidification in the prevention of cooling. In HFJV for example, at typical clinically used minute volumes, the cooling effect from the gas alone is the equivalent of about 250 kCal—about 7–10% of the daily calorie requirement. The cooling effect that would result from the use of dry gas, with the consequent latent heat losses from evaporation, would be approximately 3000–3500 kCal day^{-1}. Thus simple warming of the inspired gas would produce little clinical benefit.

Prevention of aspiration

It has been claimed that high frequency ventilation prevents aspiration of pharyngeal contents by virtue of its "auto-PEEP" effect [4, 10]. While this is largely true in paralysed, anaesthetized patients, those who are capable of voluntary inspiration or coughing can still generate a negative tracheal pressure which could result in aspiration [55]. HFV cannot be relied upon as the sole means of protecting the airway from soiling.

Ventilator–patient interfacing

HFV can be used clinically in four ventilator–patient configurations: via conventional tracheal tubes; via narrow-bore insufflation tubes; via the minitracheostomy system; via direct tracheal puncture with small bore cannulae (HFJV) [55].

There is no doubt that the ventilator–patient interface can have a marked effect upon the efficiency of gaseous exchange, particularly with HFJV [3, 55]. Each interface has its own physical properties which influence the behaviour of the gas jet to a greater or lesser degree, depending upon individual geometry. This should be borne in mind when attempting to compare the results obtained by different workers, or in the extrapolation of results obtained in animals to the clinical situation.

IS THERE A FUTURE FOR HFV?

HFPPV. There is no doubt that HFPPV can produce adequate respiratory exchange for indefinite periods in many clinical situations, but there is no evidence to show that it is superior to low frequency techniques in any clinical setting. Most of the clinical enthusiasm for this mode of HFV has come from Scandinavia, where the technique appears to be popular for endoscopy [49]. While it may be true that HFPPV provides better operating conditions than conventional IPPV in this setting, there is no objective evidence of its superiority to low frequency jet ventilation using the same small-radius catheters for gas delivery [19].

HFJV. High frequency jet ventilation has found clinical support in a number of situations. Its role in the fields of thoracic and laryngo–tracheal surgery is now firmly established [15]. Its use in abdominal surgery is less clearly defined, but it may provide better operating conditions in upper abdominal surgery because of the reduction in ventilator-related movement of the viscera in biliary surgery, and in extracorporeal shock wave lithotripsy, for similar reasons [48]. The technique is becoming popular in intracranial surgery, again because of the marked reduction in ventilator-induced movement of the brain during microscopic surgery [8]. Overall, there seems little doubt that HFJV will become commonplace in the operating theatre, one paper commenting that it "...should be included in the armamentarium of each operating room..." [40].

HFJV in intensive care. There are numerous anecdotal reports of HFJV succeeding where conventional ventilation has failed [40]. There is no doubt that HFJV can maintain ventilatory exchange in cases of major airway disruption and major air leaks following trauma or barotrauma [19, 40]. Some workers have shown that the magnitude of a leak can be reduced by HFJV, and have suggested that this could aid resolution [55]. While this would appear logical, there is as yet no evidence to support such a view.

A study of 63 patients with a variety of clinical pathologies who were ventilated with HFJV showed that many of the theoretical advantages proposed for HFJV do appear to exist clinically [55]. In particular, patients showed improved cardiovascular and renal function and, in many cases, improvement of pulmonary function when transferred from IPPV to HFJV.

In patients with increased intracranial pressure, transfer from IPPV to HFJV was associated with a significant reduction in intracranial pressure for a comparable arterial carbon dioxide tension [25]. If this reduction will prove beneficial in terms of mortality or morbidity remains entirely speculative.

Thus it seems certain that HFJV will have a clinical role for some time to come, and represents both a significant advance in therapeutics and a welcome addition to the armoury of the clinical anaesthetist.

HFO. While HFO can maintain adequate gas exchange for prolonged periods in many situations, there is as yet no clearly defined clinical role for this mode of ventilation.

A report in 1981, of a series of patients with neonatal respiratory distress syndrome treated with HFO, suggested that there was a significant improvement in oxygenation compared with that provided by conventional IPPV [33]. On closer inspection, however, the mean airway pressure generated during HFO was significantly greater than during IPPV. It has been shown that adequacy of oxygenation in respiratory distress syndrome is related to the mean intrapulmonary pressure [44], hence this result does not prove any advantage for HFO *per se*. In contrast, it is interesting to note that, despite the higher pressures involved with HFO, there was no greater degree of cardiovascular compromise compared with IPPV.

A large-scale trial in similar patients has recently been reported [7]. No significant improvement in morbidity or mortality was demonstrated in infants treated with HFO; indeed, this group showed a greater incidence of pulmonary air leak during the course of the study.

Despite the absence of any clearly defined clinical niche for HFO, there seems little doubt that it will continue to be used extensively in bench testing and animal experimentation. As mentioned earlier, this is largely because of the relative ease of analysis of the near sine wave pressure and flow characteristics of this mode, however limited this may be in terms of elucidating the fundamental physical behaviour of the respiratory tract [20].

CONCLUSIONS

HFV is here to stay. What has been disappointing in the past few years is the lack of standardization of terminology and methods. It is equally disappointing to note that, in many cases, researchers have failed to seek help from the fields of physics, mathematics, acoustics and engineering. Workers in these disciplines have developed valuable analytical methods which must be brought to the attention of enthusiastic, but somewhat amateur, clinicians. This lack of structured analysis has lead to the publication of many papers which describe facets of the curious behaviour of HFV, but without providing any physical explanation of these oddities.

Against this background, it is not surprising that many clinicians are confused about, or even intimidated by, HFV. What is urgently needed is a cohesive presentation to the clinician of the facts regarding HFV insofar as these are known, from the points of view of both basic physiology and clinical utility. The clinician is not without blame however, and it is depressing to hear that many centres have "evaluated" HFV and dismissed it. If the basic physical principles of the techniques were not understood, then perhaps they were not evaluated fairly.

It is to be hoped, however, that our patients will not be denied the undoubted benefits of HFV, and HFJV in particular, simply because the exact details of its mechanisms of action are unknown. It may be worth recalling that conventional IPPV was used effectively for many years before its physiology was elucidated.

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SLEEP APNOEA AND THE UPPER AIRWAY

V. HOFFSTEIN AND N. ZAMEL

Sleep apnoea is truly a disease of the 20th century. Snoring, which is a cardinal symptom of sleep apnoea, and its implications regarding health and well being were appreciated by Cattlin [10] in the 19th Century, and both Dickens and Shakespeare described individuals whom we would recognize as suffering from sleep apnoea. It was only in the second part of this century, however, that sleep apnoea became recognized as a distinct medical entity affecting up to 2% of the adult population [20].

Abnormalities of the structure and function of the upper airway have been firmly established as causative factors. Although the upper airway may not be *the* primary organ responsible for cessation of breathing during sleep, it is certainly the final common pathway for abnormalities in respiratory control and neuromuscular co-ordination leading to sleep apnoea. Understanding of the upper airway structure and function in affected patients may provide insights into the pathogenesis of this disorder, enable us to identify patients at risk and help us to select appropriate therapy.

Definitions

For the purposes of this review, *sleep apnoea* is defined as cessation of breathing lasting 10 s or more, while *sleep hypopnoea* is defined as a 50% reduction in tidal volume (or more) for at least 10 s; both types of episode should be accompanied by oxygen desaturation of at least 4% from the baseline value. The *apnoea/hypopnoea index* (AHI) is defined as the number of apnoeic or hypopnoeic episodes per hour of sleep. *Obstructive apnoeas* are caused by upper airway obstruction and are accompanied by continued respiratory efforts by the diaphragm. *Central apnoea* is unaccompanied by any respiratory effort. Since many normal, asymptomatic subjects exhibit obstructive and central apnoeas during sleep, we shall define sleep apnoea (somewhat arbitrarily, but conventional) as a state in which 10 or more apnoeic/hypopnoeic episodes occur per hour—that is, when AHI $\geqslant 10$. Sleep apnoea syndrome is considered to be present when there is confirmed evidence of sleep apnoea (AHI $\geqslant 10$) *plus* the presence of any of the characteristic symptoms such as excessive daytime sleepiness, snoring, morning tiredness, fatigue, headaches or nausea.

KEY WORDS

Airway. Obstruction. Sleep. apnoea.

METHODS FOR ASSESSING UPPER AIRWAY PATENCY

The flow–volume curve

This is one of the oldest methods for the assessment of upper airway patency. Specific patterns of the flow–volume loops in extrathoracic/intrathoracic and fixed/variable upper airway obstruction have been described by Miller and Hyatt [40]. The shape of the loop and the mid vital capacity flow ratio ($\dot{V}E_{50}/\dot{V}I_{50}$) show characteristic abnormalities in upper airway obstruction. Although the flow–volume curve is a simple test, its low sensitivity makes it an impractical method for the diagnosis of upper airway obstruction, because more than 50% reduction in airway diameter is required before abnormal patterns become apparent [40].

Recently, it has been suggested that patients with obstructive sleep apnoea (OSA) have variable extrathoracic airway obstruction characterized by reduced maximum inspiratory flow and increased mid vital capacity flow ratio, even while awake. It has been claimed that flow oscillations during expiration, inspiration or both are a specific feature of sleep apnoea [53]. However, studies involving large numbers of patients with OSA have demonstrated that the mid vital capacity flow ratio is similar in both apnoeic and non-apnoeic

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snorers [29] and that flow oscillations, although specific for OSA, occur in less than 10% of patients. These observations suggest that flow–volume curves have limited value in the assessment of patients with sleep apnoea.

Radiographic techniques

These techniques consist mainly of x-ray cephalometry and computed tomography of the upper airway.

X-ray cephalometry is essentially a standardized lateral radiograph of the head with a well-controlled head position. The patient is usually seated in a lateral position exactly 90° to the machine. The head position is maintained by the use of a cephalometric head-holder. From this radiograph, several measurements of the pharynx, uvula, soft palate and maxilla can be made. These relate to the size of the oropharyngeal airway and reflect the influence of malposition of the mandible on airway size. The principal value of this technique, which has been used extensively by several groups [2, 41], is to identify those anatomical abnormalities which may be amenable to surgical correction. Their results show that a high proportion of patients with sleep apnoea have morphological abnormalities of the facial skeleton and a reduction in the size of the pharyngeal airway. The technique may be useful in preoperative surgical assessment [48], but some studies have showed poor correlation between preoperative cephalometry and surgical outcome [21].

Computed tomography (CT) involves imaging thin slices of the airway from the nasopharynx up to the level of the larynx. The main value of this static technique has been to identify diffuse reductions in upper airway size in patients with sleep apnoea and to monitor changes in the upper airway size in response to various interventions, both surgical and medical [23]. Conventional CT scans have not proved to be useful in determining the site of obstruction in patients with sleep apnoea, nor in preselecting patients for surgery. A further limitation of this technique is that it does not permit dynamic studies of upper airway dimensions during breathing.

Cine-CT overcomes some of these problems by imaging one slice of the airway per 24 ms. This allows us to visualize the airway during apnoeic episodes and thereby determine the site of obstruction. Although experience with this technique is limited, it may be of value in identifying candidates for surgical correction. An ultra-fast CT scanning technique described recently [19] may also prove to be useful in this regard.

Fluoroscopy, particularly in sleeping patients with OSA, has been used to visualize the site of airway obstruction. Although this is probably the best technique for direct detection of airway closure during sleep, interpretation is somewhat subjective, it may be uncomfortable for the patient and its role in selection of patients for surgery has not been fully established. Preliminary results, however, are promising [35].

Important limitations of all radiographic techniques are their high cost and the inevitable exposure to radiation.

Magnetic resonance imaging

This is a very new technique and experience with it in the investigation of sleep apnoea is still limited. It has been used in a few selected patients with OSA to determine the distribution of fat within the airway [30] and to measure pharyngeal volume [1]. Undoubtedly, more applications of this technique for imaging the upper airways will be forthcoming.

Acoustic reflection technique

This technique is based on measurements of acoustic reflections arising from the airway in response to an incident sound wave [16]. An apparatus for the measurement of area profile by this method is shown in figure 1. Briefly, it consists of a sound source (a loudspeaker) mounted in the middle of a 2 m long wavetube, a recording microphone located near one end of the

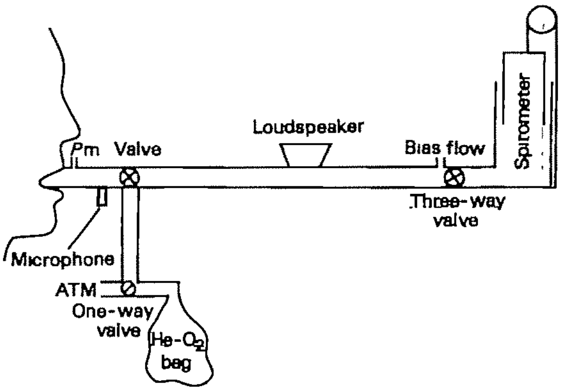

FIG. 1. Schematic diagram of an experimental arrangement for the *in vivo* estimation of tracheal distensibility and hysteresis in normal adults, using the acoustic reflection technique. *Pm* is a port for measuring mouth pressure. (Reproduced with permission from [28].)

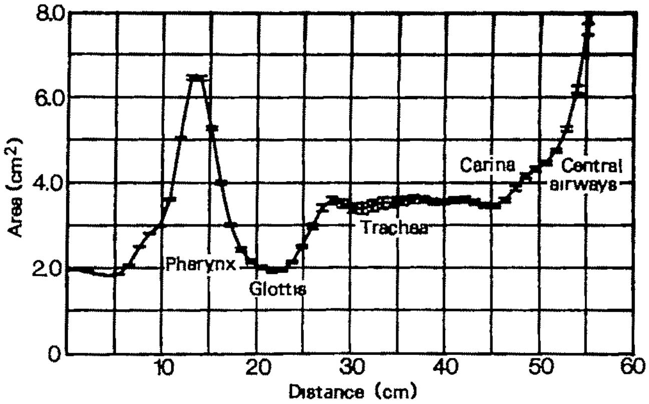

FIG. 2. Normal area–distance plot with anatomical landmarks as indicated; the plot represents the mean (SD) of 128 measurements obtained at FRC. Effect of mouthpiece, noseclips and head position on airway area measured by acoustic reflections. (Reproduced with permission from [50].)

wavetube, an amplifier and filter to process the pressure signal sensed by the microphone, and a computer for data acquisition and analysis. The subject is positioned at one end of the wavetube and a recording spirometer is located at the other. The loudspeaker emits a sound wave which travels along the wavetube and into the subject's airway, where it is reflected back towards the source. Incident and reflected waves are recorded at the mouth. From the differences in these two signals, changes in airway cross-sectional area can be inferred as a function of distance from the recording microphone. In order to achieve the required acoustic bandwidth, all measurements must be performed with the subject breathing an 80:20 mixture of helium and oxygen.

From the measurements described above it is possible to construct a plot of airway cross-sectional area *vs* distance from the mouth—the airway echogram. A typical airway echogram, obtained in a normal subject breathing at functional residual capacity (FRC) is shown in figure 2, with the regions corresponding to the pharynx, glottis and trachea indicated. This plot represents an average of 128 measurements obtained during tidal breathing at FRC. The small standard deviations indicate good reproducibility of the measurements. The technique is simple, non-invasive, has no associated radiation hazards and may be easily repeated many times in the same patient. Measurements of the entire upper airway area (from the mouth to the carina) can be made at 0.2-s intervals, permitting both static and dynamic studies of the upper airway. Figure 3 shows a series of airway echograms measured in a normal subject during quiet expiration from full inspiration down to residual volume. It is evident that the area of the entire upper airway diminishes with decreasing lung volume. These lung volume-associated changes in pharyngeal area are greatly exaggerated in patients with obstructive sleep apnoea.

The accuracy and reproducibility of this technique has been best established for the trachea, for which acoustic measurements have been compared with those made using radiography [6, 15]. It was found that the acoustic:radiographic area ratio varies between 0.94 and 1.06. The longitudinal resolution—that is, the minimum distance along the airway over which two consecutive measurements of area may be performed by this technique—is about 1.5 cm. When

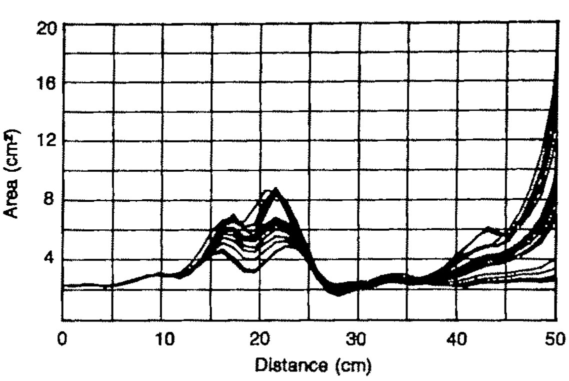

FIG. 3 Airway echograms measured during continuous slow expiration from total lung capacity to residual volume. Pharyngeal cross-sectional area in normal men and women. (Reproduced with permission from [8].)

applied to patients with tracheal stenosis, this technique was found to be superior to flow-volume curves, and the results agreed well with measurements obtained using various radiographic views and CT scans of the trachea.

The acoustic technique has been extensively applied to studies of the upper airway (pharynx, glottis and trachea) in patients with snoring or sleep apnoea, or both [5, 38, 51]. Although attractive because of its safety, speed and reproducibility, this technique has several drawbacks. It is confined to only a few laboratories, and the results await confirmation by other investigators. It cannot resolve distances less than 1 cm, and bypasses the nasopharyngeal airway which may be important in the pathogenesis of sleep apnoea. It requires some co-operation from the subject, and therefore is most applicable to awake patients. It can, however, be modified to enable measurements to be made during sleep. Some of the above problems are currently being resolved. For example, Hilberg's group [26] have used this technique to measure nasal dimensions, suggesting that the acoustic technique might be applied to the entire upper airway—from the nares to the carina.

UPPER AIRWAY ABNORMALITIES IN SLEEP APNOEA

The use of the above techniques to study upper airway dimensions, coupled with measurements of upper airway muscle activity during sleep, provided important insights into the mechanisms of upper airway obstruction during sleep.

Structure

Numerous studies using various techniques (cephalometry, CT scans, or acoustic reflections) have demonstrated that patients with OSA have reduced pharyngeal area when compared with non-apnoeic, non-snoring controls [2, 5, 19, 23, 35, 41]. In some patients obvious abnormalities such as large tonsils or adenoids, thick beefy tongue, or long and bulky uvula contribute directly to a reduced oropharyngeal space. Other patients have abnormalities such as retrognathia, micrognathia or other deformities of the jaw, which may or may not be evident on physical examination. The majority of patients with OSA do not appear to have clinically identifiable anatomical abnormalities, but may have reduced upper airway diameters when assessed by objective measurement. This reduction in pharyngeal area may be quite dramatic; CT scans show that in some patients there is almost complete pharyngeal closure, even when awake.

Reduced pharyngeal cross-sectional area found in awake, seated patients indicates that complete airway occlusion may occur during sleep. Normal physiological mechanisms which operate during sleep lead to reduced pharyngeal area by virtue of the backward displacement of the palate and the base of the tongue [47]. It is reasonable to assume that, if pharyngeal dimensions are already reduced before the onset of sleep, a further reduction during sleep may lead to complete occlusion, particularly if the function of the upper airway is also abnormal.

Function

Upper airway structure and function are interrelated and dependent on the neuromuscular control and mechanical co-ordination of the pharyngeal muscles. Pharyngeal aperture and the stability of the upper airway are determined by the position of the soft palate, tongue and hyoid arch. The equilibrium position and movements of these structures are achieved by the interaction of several muscles, the most important being the genioglossus, geniohyoid and tensor palati. During normal sleep, complex reflex mechanisms co-ordinate the interaction between thoracic and upper airway muscles, and modulate upper airway resistance in response to both mechanical loading of the upper airway (e.g. nasal obstruction) and chemical stimuli such as hypoxia and hypercapnia. The neural control of these muscles is state-dependent, with major differences in control during wakefulness and sleep. Patients with sleep apnoea usually do not occlude their upper airway while they are awake. However, the onset of sleep may lead to complete upper airway occlusion as a result of the failure of the pharyngeal dilator muscles to maintain airway patency. This is caused by reduced phasic inspiratory activity of the pharyngeal muscles, an increase in pharyngeal resistance and shifts in the pattern of activation between upper airway and thoracic muscles.

It is not possible to implicate a single muscle as being predominantly responsible for the abnormalities in pharyngeal mechanics. The genioglossus and geniohyoid muscles are important, since they pull the tongue forward and prevent it from falling passively into the pharyngeal lumen or being actively sucked into the airway by subatmospheric inspiratory pressures. Clearly, a reduction in the activity of these muscles, although not observed consistently, would promote pharyngeal occlusion. Remmers and colleagues [45] have proposed that this may be an important mechanism for airway occlusion during sleep. The tensor palati normally prevents an inspiratory prolapse of the soft palate, but shows reduced activity during sleep. The geniohyoid and sternohyoid muscles are also important, since they control the displacement of the hyoid and the position of the epiglottis, thereby affecting the patency of the hypopharyngeal airway.

We still do not know precisely which muscles relax during sleep to cause airway occlusion, which muscles are important in the relief of airway occlusion, and how the integration of these diverse muscle groups takes place [46]. Controversies and disagreements abound. Less controversial are the *consequences* of abnormal neuromuscular control in patients with sleep apnoea. Functional abnormalities of the airway walls, all of which lead to increased collapsibility of upper airways, have been well-established. It has been proposed [7] that increased collapsibility of the upper airway, coupled with reduced cross-sectional area and unopposed sub-atmospheric pressure generated by the thoracic muscles leads to complete closure of the sleeping patient's pharyngeal airway during inspiration.

The development of airway occlusion during sleep in patients with OSA is a result of the interaction between factors such as structural abnormality of the pharynx, increased collapsibility of the upper airway [32] and inability of the upper airway muscles to respond appropriately to mechanical loads, chemical and proprioceptive stimuli.

Effect of posture and lung volume

The supine posture is associated with reductions in both pharyngeal cross-sectional area and FRC, and these may be inter-related. Pharyngeal cross-sectional area varies with lung volume, although the mechanism is not clear. It may be either a reflex phenomenon or a purely mechanical event associated with thoracic traction. Whatever the mechanism, the relationship between upper airway occlusion and a reduction in FRC is indirectly confirmed by the fact that an increase in FRC appears to abolish obstructive sleep apnoea [55].

Reduced pharyngeal area in the supine position may also be a consequence of increased pressure on the neck of submental adipose tissue. This possibility is supported by common clinical observation and confirmed by the finding that patients with OSA have a greater neck circumference than non-apnoeic controls [37].

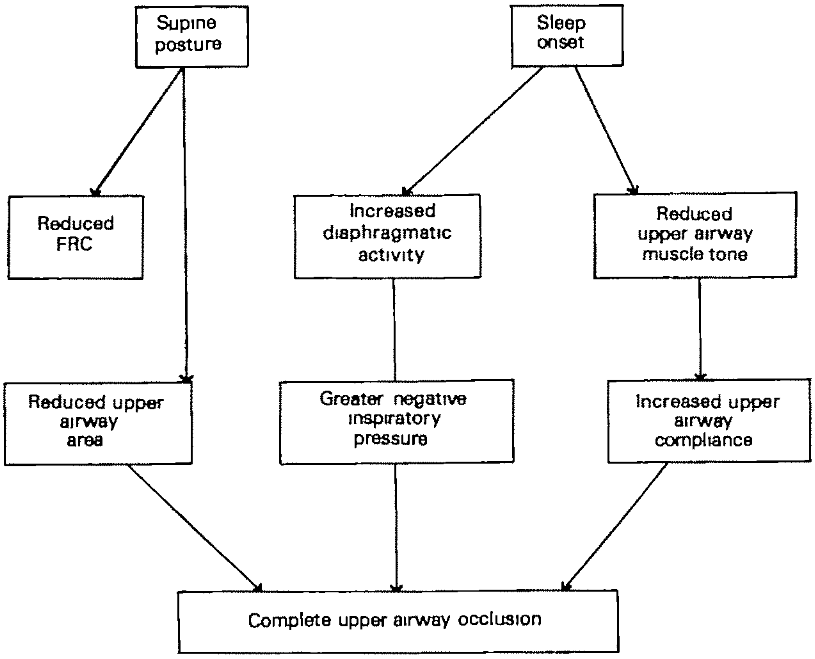
Supine posture
Sleep onset
Reduced FRC
Increased diaphragmatic activity
Reduced upper airway muscle tone
Reduced upper airway area
Greater negative inspiratory pressure
Increased upper airway compliance
Complete upper airway occlusion

FIG. 4. Factors contributing to obstructive sleep apnoea.

It is clear from the above discussion that obstruction of the upper airway during sleep is dependent on a complex interplay of factors which act to promote upper airway obstruction, as shown diagrammatically in figure 4.

Site of obstruction

Direct observations indicate that the commonest and most likely site of airway obstruction during sleep is the pharynx [4, 64]. However, the site of obstruction is by no means confined to the pharynx. Any site, from the nasopharynx to the larynx may be involved, either directly or by facilitating a more distal obstruction. Sometimes the obstruction occurs at multiple sites [64]. Rubinstein and colleagues [51] described patients with severe OSA who had paradoxical movements of the vocal cords, suggesting that laryngeal factors may contribute to the aetiology of this condition.

If direct measurements of intra-airway pressures are made in sleeping OSA patients, the obstructive site can often be identified. Hudgel [31] measured intra-airway pressures at different sites in nine patients with OSA and observed that 50% of the patients obstructed in the retropalatal region, while the rest obstructed at the base of the tongue. Chaban, Cole and Hoffstein [11] used a similar technique in 10 patients with OSA and reported similar results. The importance of such measurements in patients considered for palatal surgery cannot be over-emphasized. It is hoped that, by careful selection based on the site of obstruction, it may be possible to improve the otherwise unimpressive surgical outcome. Further studies are required in order to test this hypothesis.

TREATMENT

With an increased understanding of the pathophysiology of sleep apnoea and the crucial role played by the upper airway in the pathogenesis of this disorder, rational approaches to clinical management have emerged. While, 10 or 15 years ago, tracheotomy was the only effective treatment for severe cases, a wide variety of medicines, mechanical prostheses and surgical approaches are now available [34, 58].

Medical treatment

Sleep apnoea occurs in association with several systemic disorders such as hypothyroidism, acromegaly, uraemia, sickle cell anaemia and several others. Treatment of these disorders usually leads to resolution or significant improvement of sleep apnoea.

Probably the most valuable approach to treatment of sleep apnoea is weight reduction. The majority (60–75%) of patients with OSA are either grossly obese or significantly overweight, defined as a body mass index (BMI) greater than 27 kg m^{-2}. There are several reasons why obesity may aggravate sleep apnoea. Submucosal deposits of fat in the upper airway may interfere with the muscle–tissue linkage and contribute to an increase in pharyngeal compliance by altering the contractile behaviour of these muscles in response to neural stimuli. Fatty tissue in the neck may cause mechanical loading of the upper airway, leading to reduction in its cross-sectional area and inco-ordination between the upper airway and thoracic muscles. These patients demonstrate significantly greater lung volume-associated changes in pharyngeal cross-sectional area than do non-apnoeic controls, implying a more "floppy" pharynx. Weight loss leads to reversal of these abnormalities [61]. The precise amount of weight that must be shed in order to improve sleep apnoea varies from subject to subject. We have seen a significant improvement in OSA following only 5–10 kg weight loss. Although weight reduction should be the first advice given to patients with OSA, their compliance with the dietary programme is usually very poor. That is why surgical procedures such as gastroplasty are frequently considered. The decision regarding surgery has to be made on an individual basis, taking into account the degree of obesity, severity of apnoea, general medical condition and the patient's determination to undergo the procedure.

Many different drugs (table I) have been tried. The most studied drug has been protriptyline [9], a tricyclic antidepressant capable of suppressing REM sleep—the stage of sleep at which most apnoeas and episodes of oxygen desaturation occur. Two double-blind, placebo-controlled studies [9, 57] demonstrated that administration of protriptyline is associated with subjective improvement in daytime sleepiness and increased oxygen saturation. Sleep architecture and the AHI do not appear to be altered significantly. Anticholinergic side effects (urinary retention, dry eyes, *etc.*) are frequent and may limit the usefulness of this agent. The mechanism of improvement may be ascribed to REM suppression and augmentation of upper airway respiratory muscle activity.

TABLE I. *Drugs assessed for use in the treatment of sleep apnoea*

Drug	Action
Progesterone	Respiratory stimulant
Acetazolamide	Respiratory stimulant
Almitrine	Carotid body stimulant
Prochlorperazine	Dopaminergic antagonist
Naloxone	Opioid antagonist
Bromocriptine	Dopamine antagonist
Protriptyline	Tricyclic antidepressant, CNS stimulant
Imipramine	Tricyclic antidepressant, CNS stimulant
L-Tryptophan	Serotonin antagonist
Theophylline	Weak respiratory stimulant
Nomifensine	Dopaminergic antidepressant
Nicotine	Augments upper airway muscle activity
Strychnine	May enhance upper airway muscle activity
Doxapram	Respiratory stimulant

Other drugs used in the treatment of sleep apnoea (table I) have not been systematically studied, and evidence as to their possible benefits is largely anecdotal. In our opinion, the pharmacological treatment of sleep apnoea is of minimal value. A notable exception would be the patient with allergic rhinitis and marked nasal obstruction who develops obstructive sleep apnoea during the allergic season or as a result of occupational factors. Increased nasal resistance has been demonstrated to be an important cause of snoring and sleep apnoea [28]. In these patients, a course of nasal decongestant and antihistamines or cessation of occupational exposure may be of considerable benefit. Respiratory allergies occur in about 10% of patients with sleep apnoea, and their treatment may lead to the resolution of this syndrome.

It is important that patients with OSA avoid alcohol, sedatives, hypnotics, opioids, tranquillizers and drugs which reduce muscle tone. Any of these can convert a non-snorer into a snorer, or a non-apnoeic snorer into an apnoeic snorer, even after a single night-time administration. The mechanism is thought to be related to the relaxation of upper airway muscles in combination with respiratory depression, particularly in an obese patient.

In some, but not all patients, adoption of the lateral or even upright posture may significantly improve sleep apnoea, probably by increasing the patency of the upper airway either directly by altering the position of the tongue and soft palate and reducing the mass loading effect of neck fat, or by a reflex mechanism related to changes in FRC.

Prosthetic devices

A number of prosthetic devices have been used to increase airway dimensions during sleep. These fall into two categories: tongue retaining and mandibular positioning devices. They are designed either to keep the tongue from falling backwards or to prevent posterior displacement of the mandible. Although some reports suggest that these devices can lead to clinical improvement, none of them has yet been shown to be of definite long term benefit. Potential disadvantages include irritation of the tongue and jaw because of rigid position, forcing nasal breathing (which may be difficult), dental complications and temporo–mandibular joint pain resulting from stresses caused by the appliances.

Nasal CPAP

The greatest advance in the non-surgical treatment of sleep apnoea has been a discovery by Sullivan that a relatively low continuous positive airway pressure (CPAP), applied by a nasal mask, completely abolishes sleep apnoea in most patients [60]. The system consists of a blower, nasal mask and connecting hose; the mask fits snugly over the nose and upper lip. Oronasal masks are not used, because of discomfort. Since the first description of the apparatus in 1981, several manufacturers have introduced improved versions of the nasal CPAP system, so that now there is a wide selection of non-allergenic, washable plastic masks of different sizes, as well as light-weight, portable and quiet blowers capable of generating pressures from 2.5 to 20 cm H_2O.

It is widely recognized that nasal CPAP

markedly improves or abolishes sleep apnoea, and it has become the most commonly used non-surgical treatment for this condition. Furthermore, treatment with nasal CPAP may reverse other complications of sleep apnoea such as hypoxaemia, cardiovascular changes and sleep fragmentation. It improves neuropsychiatric function and relieves clinical symptoms such as snoring, daytime fatigue and excessive daytime sleepiness. It is remarkable that 5–10 cm H_2O of positive pressure measured at the nasal mask is capable of opening the airway completely at the distal pharyngeal site and preventing recurrent collapse.

Usually, nasal CPAP is well tolerated and the compliance rate is approximately 80%. Side effects all relate to leaks around the mask, pressure exerted by the mask, and the level of positive airway pressure; they include dry nose, occasional nose bleeds, sore eyes with occasional conjunctivitis, bruises over the ridge of the nose or on the face. Some patients feel claustrophobic and cannot tolerate the mask. CPAP is not only a useful method for the chronic management of sleep apnoea, but also may be used during pre- or postoperative management of these patients.

There are several possible mechanisms for the dramatic improvement following treatment with nasal CPAP [59]. The most likely mechanism is a "pneumatic splint effect"—that is, simply opening the airway by positive intraluminal pressure sufficient to prevent its collapse during inspiration. This mechanism was originally proposed by Sullivan and colleagues [60] and subsequently confirmed by direct endoscopic observations in sleeping patients with OSA. Other mechanisms may also be operative. CPAP increases FRC and it is possible that this has a reflex or direct action on the upper airways, leading to an increase in their cross-sectional area. Finally, positive intra-airway pressure may lead to reflex activation of pharyngeal muscles, causing widening and stiffening of the pharyngeal airway. Whatever the mechanism, CPAP remains the treatment of choice for many patients with sleep apnoea, regardless of the severity of the disorder, and has the highest success rate of any non-surgical treatment.

Surgical correction

The choice of surgical procedure should be based upon the anatomical deformity in each patient. Specific surgical procedures are indicated by conditions such as deviated nasal septum, large tonsils or adenoids and mandibular deformity or malposition. However, definite anatomical abnormalities can be found in less that 15% of patients with sleep apnoea. In most patients no obvious anatomical deformity can be demonstrated, and they are said to have idiopathic obstructive sleep apnoea. Several different surgical procedures are currently performed in such patients.

Tracheotomy is probably the oldest and the most beneficial procedure, with a high success rate [22]. It bypasses the site of airway obstruction, which is always supraglottic. Insertion of the tracheostomy and relief of airway obstruction not only leads to prompt resolution of sleep apnoea, but also to marked improvement in hypoxaemia, hypertension and sleep architecture. Although effective, this procedure has fallen into disfavour because of poor patient acceptance associated with both acute and long term side effects. The major reasons for this are: chronic cough, interference with speech, irritation at the tracheostomy site, occasional local bleeding, recurrent episodes of bronchial irritation and infection resulting from bypassing normal humidification and filtering mechanisms, difficulty managing secretions, social embarrassment and reactive depression. Although tracheotomy is a relatively safe procedure, a few deaths have been described. Proper surgical technique is important, since most patients are obese with short, fat necks, which makes the insertion and maintenance of the tracheostomy more difficult. Care must be exercised with preoperative medication, since some of these patients are very sensitive to sedative agents [43]. There are few indications for tracheotomy today and it is reserved for patients with severe obstructive sleep apnoea in whom other measures are ineffective or cannot be tolerated. It may be useful in the patient who requires a temporary urgent relief of OSA while awaiting a definitive procedure. In such cases, insertion of a 5-mm minitracheostomy tube may be a satisfactory alternative to a formal tracheostomy [24]. Sleep studies should be performed within a few weeks following tracheotomy, because relief of obstructive apnoea may expose other sleep-related problems such as hypoventilation, central sleep apnoea or nocturnal myoclonus.

The most commonly performed surgical procedure for treatment of idiopathic OSA is uvulopalatopharyngoplasty (UPPP), originally described by Fujita and colleagues [18]. This operation involves removal of the uvula and tonsils, partial resection of the soft palate and resection of redundant pharyngeal tissue. Following operation there is an increase in pharyngeal area and "stiffening" of the pharyngeal walls. Most of the initial reports were enthusiastic [18, 25, 56], suggesting that clinical improvement could be achieved in up to 85% of OSA patients. These studies, however, did not involve long follow up periods and did not always include proper assessments of airway patency.

The assessment of outcome following UPPP is complicated by a lack of standard criteria for the assessment of outcome [54]. For instance, should success be based upon subjective improvement in symptoms, improvement in the AHI, improvement in oxygen saturation, improvement in sleep architecture, or a combination of all these indices? Even today, there is no agreement as to the most appropriate criteria. For example, if a 50% reduction in AHI is used as the sole criterion of improvement, then Fujita's own follow-up study of patients with UPPP [2] indicates a zero success rate, since the mean index improved only from 59 to 31! This is consistent with other studies showing relatively little change as judged by this criterion [3, 36, 63]. Some investigators, however, reported a significant reduction in AHI following surgery [39]. These divergent results are attributable to small sample sizes, differences in surgical techniques, differences in follow-up methods and differences in assessing outcome. Not all patients benefit from UPPP to the same extent. For example, Conway and colleagues [13] reported clinical improvement in 50% of the patients undergoing UPPP, using "more than 50% reduction in AHI within 6 weeks after surgery" as their criterion. Gislason and colleagues [21] found that 65% of patients improved within 6 months following UPPP. Patients who do not respond to UPPP are usually more obese, have milder disease and tend to obstruct near the base of the tongue or more distally, rather than in the retropalatal region. Several studies noted disagreement between the subjective assessment by the patient and the more objective polysomnographic results. For example, Regenstein and colleagues [44] obtained subjective sleepiness scores and performed polysomnography in 40 patients with OSA before and after upper airway surgery; none showed any improvement by polysomnographic criteria, but 27 out of 40 reported greater than 50% improvement in their sleepiness scores.

The lack of consistency, so far as the effectiveness of UPPP is concerned, is probably related to differences in surgical technique, body weight and age, site of airway obstruction and methods of assessment. Furthermore, despite the use of criteria based on cephalometry, CT scans, somnofluoroscopy and response to the Mueller manoeuvre [33], it is possible that we still do not select the right patients for UPPP.

The main complications included oropharyngeal haemorrhage, transient nasopharyngeal reflux and rhinolalia, oropharyngeal infection and palatal stenosis. These complications are infrequent, ranging from none to about 10% in various series [13, 14, 16, 17, 21, 24, 36, 39, 44, 45, 63].

Surgical procedures other than UPPP have also been performed in patients with idiopathic OSA. Riley and colleagues [49] recently described inferior sagittal mandibular osteotomy and hyoid myotomy in 55 patients. Most of these were selected by presurgical assessment of the site of obstruction (distal oropharynx and hypopharynx, or base of the tongue), or had failed to improve following UPPP. Of those operated upon, 67% were considered to have a beneficial response at 6 months following surgery.

Anaesthesia for upper airway surgery may present a number of problems [12, 43, 62]. In the period immediately before operation it is important to ensure that concomitant medical problems such as chronic lung disease, heart failure or pulmonary hypertension are treated appropriately to provide maximum bronchodilatation and oxygenation. Before operation, sleep apnoea should be treated with CPAP, or if this is impossible and the apnoeas are severe with marked oxygen desaturation or arrhythmias, or both, a temporary tracheotomy should be performed. Preoperative sedation with tranquillizers or opioids should be avoided.

During the immediate postoperative period there may be an increased risk of upper airway obstruction as a result of atonia of upper airway muscles (induced by anaesthesia) and pharyngeal oedema. Early postoperative deaths have been reported, indicating that the tracheostomy should be left in place until the airway stabilizes. However, several reports have suggested that unselected postoperative tracheostomy is unnecessary. Sanders and colleagues [52] performed polysomnography in 10 patients with OSA on the second day following UPPP and found no significant difference in AHI compared with the preoperative values. Although there was a significant increase in the alveolar–arterial oxygen gradient following UPPP, the hypoxaemia could be well controlled with supplementary oxygen without any adverse effects on $P\text{CO}_2$ or the number of apnoeas. Similarly, Powell and colleagues [42] found that even patients with severe sleep apnoea could be adequately managed with supplementary oxygen alone. Furthermore, these authors showed that such patients are capable of tolerating nasal CPAP at a mean pressure of 13.5 cm H_2O immediately after surgery without difficulty; the use of nasal CPAP in these patients significantly reduced the requirements for supplementary oxygen. We routinely manage patients undergoing UPPP in an acute-care unit with 24-h monitoring of ECG and oxygen saturation. We no longer maintain a nasopharyngeal tube for 24 h. If necessary, we commence nasal CPAP immediately after surgery.

CONCLUSIONS AND CONTROVERSIES

We have described the role of the upper airways in sleep apnoea and how various procedures influencing upper airway patency may be useful in the treatment of this disorder. Although the upper airway is the general site of pathology, we still do not understand all the factors which influence its behaviour. Of the several treatments for the idiopathic obstructive sleep apnoea, none is fully satisfactory: the patient must either tolerate a CPAP mask or undergo a surgical procedure the success rate of which is probably no better than 50%.

Many unanswered questions and controversies still remain, and the natural course and prognosis of OSA still requires further definition. What are the factors leading to the development of OSA, and why do only some obese patients develop this disorder? What is the mechanism by which the activities of diverse muscle groups are altered so that normal, physiological narrowing of the upper airway during sleep progresses to complete occlusion? Why do only some patients benefit from upper airway surgery and how can we preselect candidates for surgery? Is it possible to screen for OSA with daytime tests performed in awake subjects? Although some of these issues have been addressed, the results are frequently inconsistent and contradictory.

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British Journal of Anaesthesia 1990; **65**: 151–152

CORRESPONDENCE

TRANSDERMAL HYOSCINE AND POSTOPERATIVE NAUSEA AND VOMITING

Sir,—Koski and colleagues [1] found no difference in the incidence of nausea and vomiting in patients receiving transdermal hyoscine or placebo before operation. This is at variance with the findings of others [2].

A number of points warrant mention. In the study of Koski, different types of surgery were performed, whereas only patients having gynaecological surgery were studied by Uppington, Dunnet and Blogg [2]. It has been noted that the incidence of nausea and vomiting differs depending upon the type of surgery undertaken—for example, 40–70% for intra-abdominal, 20–50% for gynaecological and 15% for surface/limb operations [3].

The dose of fentanyl given may have differed from that given by Uppington and colleagues, who used 3–5 μg kg^{-1}. What was the dose range in the current study?

The assessment of nausea and vomiting, although estimated on a similar scale, was made by an unspecified number of recovery nurses in the Koski study whereas, at most, only three observers made assessments in the study of Uppington and colleagues.

Finally, the fluid regimen differed in the two studies: 2–5 ml kg^{-1} h^{-1} (Koski) and 5–10 ml kg^{-1} h^{-1} (Uppington).

The aetiology of nausea and vomiting is multifactorial [3]. The study by Koski and colleagues failed to demonstrate a difference between transdermal hyoscine and placebo. However, the differences highlighted above should be noted before dismissing the value of transdermal hyoscine as a prophylactic against nausea and vomiting for some types of surgery.

G. A. Francis
London

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Sir,—In our study, 53% of the operations were gynaecological laparotomy, 28% upper abdominal and the remainder mostly thyroid or breast surgery. We studied carefully the incidence of nausea and vomiting within the subgroups and found no statistically significant difference between the placebo or hyoscine groups.

The dose of fentanyl was 3–5 μg kg^{-1}, as in the study by Uppington and colleagues [1].

The possible bias between the nurses' estimation of nausea and vomiting was avoided by the standardized monitoring method. Nausea was recorded using the following grading: 3 = vomiting patient; 2 = patient experiencing and spontaneously complaining of feeling nausea; if no nausea was noted, the nurses asked the patients: "Do you feel nauseated?" A positive answer was graded as 1 and a negative answer as 0.

The fluid infusion in our study was given in such a manner as to maintain normovolaemia and fulfil the normal daily fluid requirement.

E. M. J. Koski
Kuopio, Finland

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UNPREDICTABLE SPINAL ANAESTHESIA

Sir,—One of the criticisms that continues to be levelled against the use of plain 0.5% bupivacaine for spinal anaesthesia is unpredictable spread of anaesthesia and, in particular, inadequately low blocks in some patients. The work of Bannister, McClure and Wildsmith, using the smallest concentration of glucose (0.33%), supports this view—as does previous work by Logan, McClure and Wildsmith [1,2] However, they unjustly malign plain 0.5% bupivacaine as an agent for spinal anaesthesia. When it is administered to patients in the seated rather than the lateral position which they have used, adequate levels of analgesia are attained readily with plain 0.5% bupivacaine [3]. Furthermore, plain is more predictable than hyperbaric 0.5% bupivacaine when used in this way [3].

Undoubtedly, both plain and hyperbaric solutions of bupivacaine are valuable agents for spinal anaesthesia. However, appropriate positioning for lumbar puncture is required to obtain the best results from both agents.

R. P. Alston
Glasgow

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Sir,—Dr Alston's findings show that plain and hyperbaric bupivacaine produce *equally* predictable levels of sensory block when given intrathecally to the seated patient [1]. Our study showed that predictability may be obtained with lumbar puncture in the lateral position without unacceptably high blocks [2]. Many practitioners find the lateral position more convenient, especially in patients with restricted mobility, rather than sitting and maintaining that position for 2 min as recommended by Dr Alston.

Clearly, both techniques may be used as appropriate to achieve the desired effect.

J. Bannister
Dundee

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EXTRADURAL SOMATOSTATIN

Sir,—The report by Desborough and colleagues [1] of the use of extradural somatostatin in postoperative pain was read with some concern. Currently there is a body of peer-reviewed literature which suggests that somatostatin 1–14 administered spinally in three different species may have an irreversible, deleterious effect on spinal tissue [2–7] at doses less than those which produce analgesia.

Animal studies might be deemed sufficiently different (multiple dosing, higher concentration, intrathecal route) as not to be relevant to human studies. I could accept this rationale if the mechanisms of toxicity were known, and excluded in humans. Indeed, I should be enthusiastic about a blinded, well-controlled study such as that reported by these authors, particularly as it confirmed the behavioural relevance of animal models which also failed to detect an analgesic effect of spinal somatostatin 1–14. However, without information to the contrary regarding mechanisms of toxicity, I wonder why an Institutional Hospital Ethics Committee approved a drug for which the side effects were not documented and for which the use is not indicated exclusively (as, for example, the use of a potentially lethal chemotherapeutic agent in cancer) in a population of healthy patients, and what information had been conveyed to the patient in the informed consent? I do not think that one may place reliance on previous uncontrolled clinical studies, which themselves proceeded in man without the benefit of knowledge of mechanism, as being supportive of continued human investigation.

A small additional query relates to the nature of the molecule used, its vehicle and source. Somatostatin is the name given to a family of peptides that range from 14 to 28 amino acids and have different properties. These peptides may be diluted with salts and other products from the synthesis and therefore, the source and vehicle should be quoted.

T. L. Yaksh
San Diego

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Sir,—Our study was carried out between July 1987 and April 1988 after Ethics Committee approval was granted on July 20, 1987. None of the publications concerning neurotoxicity were available before our submission to the Ethics Committee or during the study.

The Ethics Committee and the patients were informed that somatostatin had been given by the extradural and intrathecal route in human studies and had been reported to be effective in the treatment of acute and chronic pain without side effects.

The study proceeded with the full knowledge and support of Serono U.K., the suppliers of the somatostatin 1–14 which was a freeze-dried, lyophilized preparation diluted in 0.9% sodium chloride.

We agree that the studies quoted by Professor Yaksh deal with neurotoxicity resulting from *intrathecal* administration of somatostatin in different species and cannot be related directly to human studies using extradural somatostatin. None of the patients in our study suffered any neurological sequelae.

However, we pointed out in our discussion the more recent work by Gauman and Yaksh [1] and Mollenholt and colleagues [2] and we stated "possible toxic effects suggest that its further use in clinical practice is unjustifiable".

J. Desborough
London

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BOOK REVIEWS

Recent Advances in Anaesthesia and Analgesia, No. 16. Edited by R. S. Atkinson and A. P. Adams. Published by Churchill Livingstone, Edinburgh. Pp. 215; indexed. Price £16.50.

I do not know precisely when this familiar and much loved series first appeared, but the publication of number 16 some 4 years after the last edition leaves one to ponder on its future role. The book consists of the established format of a collection of chapters/review articles, in this case 11, covering a variety of subjects—sedation, pain, neuromuscular block monitoring, trauma, *etc.* All except one are written or co-authored by an anaesthetist. The range of subjects covered is wide and reflects the diversity of activities in which anaesthetists are involved.

The chapters are written competently, but the authors seem to try to cover the whole subject, as in a standard textbook. As there is not the space available in a standard textbook, the overall effect is somewhat superficial. A series entitled "recent advances" should surely start where the standard textbooks end and not cover the same ground; it also needs to be published more frequently than once every 4 years. Some of the heavyweight tomes in our specialty are appearing not less frequently and covering a wider area and in greater depth. With the plethora of journals, and the recent appearance of journals consisting exclusively of reviews, together with another series similar to this but published more frequently, *Recent Advances ... No. 16* looks slightly antiquated.

Nonetheless, this is a clearly and well written book. There are a few problems: Brian Hills, who writes on alveolar models, has always been a difficult author for the non-specialist; as usual, the fluids chapter fails to differentiate between fluids chosen for resuscitation and those for intra-operative support, and I find it strange that the combination of local and "light general anaesthesia" is being hailed as a technique introduced "within the last decade". John Sear writes extremely well, but his contribution on pharmacokinetics is more comprehensible to those with numerate skills.

The content of this book will be of interest to all, particularly the examination candidate, if only on the assumption that it may well have been read recently by the examiner as it is a recent addition to an old and much loved series.

I. T. Campbell

Norris and Campbell's Anaesthetics, Resuscitation and Intensive Care, 7th Edn. By D. Campbell and A. A. Spence. Published (1990) by Churchill-Livingstone, Edinburgh. Pp. 254; indexed; illustrated. Price £9.50.

Consultant Senior Lecturers may not be the correct reviewers of books on anaesthesia written for medical students. I thought this book was a good read that gave a good idea of what anaesthesia was all about. A medical student with me on an operating list complained that it did not contain enough meat, that the lectures and tutorials she had received were more detailed and that the book was inadequate as preparation for her forthcoming examination.

She is correct, but it depends what the student wants. The sleeve notes describe "an introductory text (that) presents a clear and concise account of the different types of anaesthesia" and it does this well. The "meat" of anaesthesia comprises applied aspects of each of physics, physiology, pharmacology and clinical medicine, and the inclusion of detail from these subjects would make the book longer, necessarily more dogmatic, and less readable. The problem of what exactly should be contained in a book for students makes one wonder what they learn elsewhere in the course. Many of the students that I teach seem to have difficulty understanding the relation between the partial pressure of oxygen and its content in arterial blood; surely this is taught in preclinical physiology? My student complained that Campbell and Spence's book did not explain how to assess a patient with asthma, but what had she learned on her medical firm?

This latest edition of *Anaesthetics, Resuscitation and Intensive Care* is the seventh. If the authors want to find space for some bodybuilding in the eighth, they could omit some of the figures and diagrams. Some of the photographs are poor, and even on the shortest anaesthetic course students are shown i.v. needles and tracheal tubes.

Most of the authors' suggestions on management are sensible, although I disagree that the need to use one's fingers to open the mouth during laryngoscopy is a sign of incorrect positioning, and it is a pity that the usefulness was not stressed of anterior displacement of the mandible as a way to relieve airway obstruction.

There are details that need correcting or adding. It is no longer the general rule that all patients undergoing abdominal surgery need chest x-rays; bicarbonate is not given routinely during cardiopulmonary resuscitation; there is no mention that bupivacaine must not be used for Bier's block; and contradictory advice is given on the treatment of convulsions caused by overdose with local anaesthetic drugs. While the chapter on ITU is titled "The respiratory intensive care unit", it would have been improved by the inclusion of a short description of inotropic therapy.

Perhaps because this is a seventh edition, the book lacks tightness in places. Vasopressors are mentioned twice in the text, but with throwaway remarks: "a suitable dose of a vasopressor such as ephedrine may be given," and, "by giving a vasopressor drug such as methoxamine." Neither of these drugs, nor the term *vasopressor*, is in the index, although *dehydrobenzperidol* and *droperidol* both are.

The authors are too fond of *in the case of* and tend to write *employ* for *use* (contrary to the best advice of this journal!), but a serious error of style in 1990 is the use for most of the book of the masculine pronouns *he* and *him*. The easiest solution is to write in the plural; and to allow the child on page 22 to return to its parent, not its mother.

My first thought is still my final thought; this book is a good read, and good value for a short undergraduate course in anaesthetics. With fewer diagrams and more facts it could be a very good book indeed.

N. Goodman

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"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL

CARBON DIOXIDE CYLINDERS ON ANAESTHETIC APPARATUS

The United Kingdom and a few other countries stand apart from the rest of the world of anaesthesia in having carbon dioxide cylinders mounted on anaesthetic apparatus, and with a flowmeter which admits carbon dioxide to the fresh gas supply, a practice dating from at least 1927. Logic is not always the deciding factor in such differences in practice, and this is an appropriate time to consider the arguments for and against the presence of cylinders of carbon dioxide. In July 1989, the Department of Health in the U.K. issued *Safety Action Bulletin No. 49* which drew the attention of anaesthetists to another case of inadvertent administration of carbon dioxide, this time resulting in serious injury to the patient.

The sole purpose of exogenous carbon dioxide in anaesthesia is to increase the patient's Pa_{co_2}. This has many effects, including increasing cerebral blood flow, but the most relevant is to stimulate breathing. Historically, carbon dioxide entered the anaesthetic armamentarium for the purpose of accelerating induction with inhalation anaesthetics of high blood solubility, particularly diethyl ether. Surprisingly, 144 of the 1100 anaesthetists responding to the survey of Razis [1] still used carbon dioxide to speed induction with inhalation anaesthetics. However, as this indication has declined in response to the decreasing blood solubility of more recently developed anaesthetics, a new indication for carbon dioxide has taken its place.

During anaesthesia with paralysis and artificial ventilation, there is a tendency to overventilate, which is manifestly safer than underventilation. It is a common observation that arterial $P\text{co}_2$ values during anaesthesia with unmonitored artificial ventilation are below normal, often below the apnoeic threshold of $P\text{co}_2$, and sometimes as low as 2 kPa. This is of particular relevance now we know that inhalation anaesthetics abolish the peripheral chemoreceptor ventilatory drive and have a profound effect even at 0.1 MAC [2]. The use of high concentrations of oxygen at the end of anaesthesia also suppresses peripheral chemoreceptor drive. Thus a hypocapnic patient may be totally devoid of chemoreceptor drive at the end of a period of anaesthesia with artificial ventilation.

Under these adverse conditions of chemoreceptor drive, spontaneous breathing may be re-established by the simple expedient of allowing consciousness to be regained. In most patients, $P\text{co}_2$ less than the apnoeic threshold does not inhibit breathing when consciousness has been regained [3], although it does prevent breathing during anaesthesia. Alternatively, the re-establishment of spontaneous breathing may be hastened usually by increasing the $P\text{co}_2$ to a value greater than the apnoeic threshold, so restoring central chemoreceptor drive before consciousness is regained, and typically while the surgical wound is being closed. This can be achieved in three ways. First, the alveolar ventilation may be reduced. Second, carbon dioxide may be re-breathed by taking the soda-lime out of circuit. Third, exogenous carbon dioxide may be administered.

The time course of increase in $P\text{co}_2$ by each of these expedients was examined by Ivanov and Nunn [4]. The first method is very slow and the time course of *increasing* $P\text{co}_2$ by *decreasing* alveolar ventilation is not the mirror image of *decreasing* $P\text{co}_2$ by *increasing* alveolar ventilation. The latter is a matter of washing out body stores of carbon dioxide (with a half-time of about 4 min), while the former depends on the metabolic production of carbon dioxide, and the half-time of the resultant increase in $P\text{co}_2$ may be as long as 15 min, with an initial increase limited to a maximum of about 0.6 kPa min^{-1}. Clearly, this is rather a slow method of increasing $P\text{co}_2$ at the end of an operation when the patient has been hypocapnic for a long time. However, the situation is changed when end-tidal $P\mathrm{CO}_2$ is monitored. This permits $P\mathrm{CO}_2$ to be maintained close to normal throughout surgery and to be brought above the apnoeic threshold in anticipation of resumption of breathing. However, restriction of ventilation has other effects, particularly on uptake of a volatile anaesthetic and on arterial $P\mathrm{O}_2$, the latter being affected both by alveolar ventilation and by development of pulmonary collapse. However, ventilation and $P\mathrm{CO}_2$ may be varied independently by such means as the introduction of apparatus deadspace, or restriction of fresh gas flow in systems which permit variable rebreathing. These systems include circles without soda-lime and the Bain system. Monitoring of $P\mathrm{CO}_2$ is essential for best results with such arrangements.

The second method (bypassing the soda-lime) depends on the retention of a part of the metabolically produced carbon dioxide and is little faster than the first method [4]. The third and final method (addition of exogenous carbon dioxide) increases $P\mathrm{CO}_2$ to any required value in less than 1 min [4] and is manifestly the quickest and most controllable method of increasing $P\mathrm{CO}_2$.

There is no doubt that the presence of a cylinder of carbon dioxide on the anaesthetic apparatus exposes the patient to the risk of accidental administration of very high concentrations of carbon dioxide. In Razis' survey, 200 respondents knew of an accident with carbon dioxide that occurred in the hospital at which they currently worked: 29% of these accidents resulted in death. However, it seemed possible that the same incident might have been reported by more than one respondent. The same author reviewed nine cases of carbon dioxide-related deaths and cases of cerebral damage reported by various authors in the period 1950–1977. The danger lies in the bobbin moving to the top of the carbon dioxide flowmeter, where it may be unnoticed.

There is widespread recognition of the hazard of inadvertent administration of carbon dioxide. Furthermore, the incidence of this hazard appears to be greater than that of some of the rare complications of anaesthesia which have generated much more publicity and a great deal of research activity. Razis found that, in spite of recognition of the hazard, more than 60.9% of U.K. anaesthetists included in his survey still used carbon dioxide daily and another 20.4% did so at least once a week [1]. Withdrawal of carbon dioxide would be objectionable to 77.1% of his respondents—a figure virtually identical to that elicited at a Symposium of the Association of Anaesthetists on "The place of carbon dioxide in anaesthesia", held on December 14, 1989 under the Chairmanship of Dr R. Greenbaum.

There appear to be two solutions to this dilemma. The first is to remove the cylinder from the apparatus except when it is required for administration. However, this relies on human compliance and might engender misplaced confidence. The second solution is the imposition of a flow restrictor, limiting flow to (say) 500 ml min^{-1} in the gas lead to the carbon dioxide flowmeter. This would have two advantages: first, it would restrict the total flow of carbon dioxide to a value which is unlikely to be dangerous; second, the range of the carbon dioxide flowmeter is such that the bobbin could not rise above the mid point of the scale, where its presence could hardly pass unnoticed. This simple modification would appear to resolve the dilemma. *Safety Action Bulletin No. 49* recommends that the limiting flow rate of 500 ml min^{-1} should be halfway up the flowmeter tube. This would require development of a new flowmeter tube and it would be unfortunate if introduction of flow restrictors were delayed by development of a 1-litre carbon dioxide flowmeter tube.

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TOTAL I.V. ANAESTHESIA WITH PROPOFOL AND ALFENTANIL: DOSE REQUIREMENTS FOR PROPOFOL AND THE EFFECT OF PREMEDICATION WITH CLONIDINE†

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SUMMARY

We determined in 51 healthy patients undergoing body surface surgery the dose requirements for propofol, as part of a total i.v. anaesthesia technique with an alfentanil infusion. After premedication with temazepam, patients received alfentanil 50 µg kg⁻¹ followed by an infusion of 50 µg kg⁻¹ h⁻¹. Patients were anaesthetized with a loading dose of propofol followed by a three-stage infusion designed to reach one of five preselected blood concentrations of propofol. The motor response to the initial surgical incision was noted and probit analysis was used to derive the ED_{50} *(2.94 mg kg⁻¹ h⁻¹; 95% confidence limits: 2.35–3.37 mg kg⁻¹ h⁻¹) and* ED_{95} *(4.98 mg kg⁻¹ h⁻¹; 95% limits: 4.13–8.8 mg kg⁻¹ h⁻¹) for the final propolol infusion rate under these conditions. Whole blood concentration of propofol at the time of the incision was related linearly to the infusion rate and the* EC_{50} *and* EC_{95} *(probit analysis) were derived as 1.44 (95% confidence limits 0.62–1.87) and 4.05 (95% confidence limits 2.78–30.5) µg ml⁻¹, respectively. Postoperative recovery was rapid, uncomplicated and uneventful. In a subgroup of eight patients, the addition of clonidine 0.6 mg to the premedication significantly decreased the requirement for propofol ($P < 0.05$) during surgery, but resulted in prolonged recovery times.*

KEY WORDS

Anaesthetics intravenous propofol Analgesics opioid. alfentanil. Anaesthetic techniques· infusion Sympathetic nervous system: clonidine

Propofol has become widely established as a drug suitable for both induction and maintenance of anaesthesia, alone [2], as a supplement to nitrous oxide [3–5], or with opioids such as fentanyl or alfentanil to provide total i.v. anaesthesia [6–9]. The dose requirements for a continuous infusion of propofol to supplement nitrous oxide have been determined in patients premedicated with morphine [10] or lorazepam [11]. Early clinical trials of total i.v. anaesthesia with a combination of propofol and alfentanil [6–8] were based on empirically determined infusion rates, and did not explore specific dose–response relationships for the two drugs.

Previous studies using an infusion of alfentanil to supplement nitrous oxide anaesthesia established that a loading dose of 50 µg kg⁻¹ followed by an infusion of 50 µg kg⁻¹ h⁻¹ produced satisfactory conditions for surgery [12, 13]. We have therefore used this infusion scheme for alfentanil as the basis of a total i.v. anaesthesia technique and have determined the propofol requirements to suppress movement in response to surgical incision as an index of adequacy of anaesthesia. In order to determine these responses under conditions of stable blood concentrations of propofol, we utilized a manual infusion scheme [14] based on a previous computer-controlled infusion scheme [15].

As clonidine has been shown to decrease requirements for volatile anaesthetics [16, 17] we also determined the effect of premedication with oral clonidine on the movement response of

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†Pilot study presented to the Anaesthetic Research Society, June 24, 1988 [1].

TABLE I. *Propofol infusion schemes: loading dose and subsequent infusion rates, duration of infusion (mean (range)) and number of non-movers according to group*

	Group 1 ($n = 10$)	Group 2 ($n = 10$)	Group 3 ($n = 10$)	Group 4 ($n = 11$)	Group 5 ($n = 10$)
Loading dose (mg kg^{-1})	0.4	0.5	0.6	0.75	1.0
Subsequent infusion (mg kg^{-1} h^{-1})					
Rate 1	4.0	5.0	6.0	7.5	10
Rate 2	3 2	4.0	4.8	6.0	8.0
Rate 3	2 4	3.0	3.6	4.5	6.0
Duration of infusion (min)	56 (27–73)	36 (15–60)	53 (29–81)	39 (15–65)	44 (21–55)
Non-movers	3	5	7	10	10

patients receiving the ED_{50} infusion rate of propofol.

PATIENTS AND METHODS

Healthy patients presenting for body surface surgery (herniorrhaphy, varicose vein surgery) gave informed consent to the studies, which were approved by the District Ethics Committee. Fifty-one patients were allocated sequentially to one of five groups, each to receive differing infusions of propofol (table I) designed to achieve a stable blood concentration of propofol within 10 min and to maintain that concentration throughout the period of anaesthesia [14].

All patients were premedicated with temazepam 20 or 30 mg according to their weight, 2 h before anaesthesia. An i.v. cannula was inserted into a wrist under local anaesthesia. Two 50-ml syringes, one primed with propofol 10 mg ml^{-1} and the other with alfentanil 500 μg ml^{-1}, in calibrated Vickers IP4 drivers, were connected by a three-way tap to the cannula hub to achieve minimum deadspace. Patient monitoring consisted of ECG (CM5), automatic non-invasive arterial blood pressure measurement (Dinamap 845, Critikon), end-tidal carbon dioxide concentration (Datex) and neuromuscular transmission (Relaxograph, Datex).

Preinduction resting heart rate and arterial pressure were recorded. Anaesthesia was induced with a loading dose of alfentanil 50 μg kg^{-1} followed immediately by the appropriate loading dose of propofol (table I). A maintenance infusion of alfentanil 50 μg kg^{-1} h^{-1}, and the appropriate first stage of the three-stage propofol infusion were then started. The first and second stages of the propofol infusion were maintained for 10 min each before being decreased to the final maintenance infusion rate.

Patients' lungs were ventilated initially with 100% oxygen and, upon loss of consciousness, they were given suxamethonium 1 mg kg^{-1} to facilitate tracheal intubation. Subsequently, the lungs were ventilated with oxygen-enriched air ($F\text{I}_{\text{O}_2}$ 0.3) using an Oxford–Penlon ventilator and adjusting rate and tidal volume to produce an end-tidal $P\text{CO}_2$ of 4.8–5.2 kPa.

Confirmation of the spontaneous reversal of neuromuscular block was obtained before commencement of surgery. The patient's motor response to the initial surgical incision (groin) was noted as either movement or non-movement. A venous blood sample (5 ml into tubes containing potassium oxalate) was taken and stored at 4 °C for subsequent analysis of the whole blood concentration of propofol by high pressure liquid chromatography [18]. If the patient moved at any time following the initial incision, 20-mg incremental doses of propofol were given to allow surgery to proceed, but only after the blood sample had been taken for estimation of whole blood concentration of propofol. On completion of the surgical procedure, both infusions were discontinued and the times taken to extubation, response to command and correct recall of date of birth were recorded. During the recovery period all patients received oxygen-enriched air by face mask.

Subsequent to the calculations of the parameters (ED_{50}, ED_{95}) derived from the probit analysis of the data on the first 51 patients, a further group of eight patients received clonidine 0.6 mg with their temazepam premedication. These patients were studied in a manner otherwise identical to the first group of patients. They received the same loading dose and subsequent infusion scheme for propofol as the patients in group 2 of the first study, this dose being equivalent to the calculated ED_{50} dose for propofol.

All patients were seen at follow-up 24 h after operation and questioned about possible complications, with specific reference to pain on injection, nausea and vomiting, recall and subjective impression of the experience. The vein used for the infusion was examined for evidence of thrombophlebitis.

Statistical analysis

Population characteristics, infusion times and percentage changes in arterial pressure and heart rate were compared using the Kruskal–Wallis statistic and differences were isolated with repeated Mann–Whitney tests with a correction for Bonferroni inequality. The recovery times, being right-skewed, were subjected to logarithmic transformation before analysis. The percentage of movers : non-movers between the clonidine subgroup and group 2 was analysed using the Fisher exact test.

Probit analysis [19, 20] (SAS Institute, Cary, N. Carolina) of the proportion of non-movers at each dose rate (groups 1–5 only) was used to determine the ED_{50} and ED_{95} (final infusion rate) of propofol when combined with this particular alfentanil scheme, and to determine the EC_{50} and EC_{95} values relating effect to the whole blood concentration of propofol. Linear regression analysis was used to assess the correlation between the whole blood concentration of propofol at incision and the rate of infusion.

RESULTS

There were no significant differences of age and weight (table II), or duration of infusion (table I) between the groups.

Probit analysis of the final infusion rate and the suppression of the motor response to the initial surgical stimulus (table I) is shown in figure 1. The ED_{50} for the final infusion rate of propofol was determined as 2.94 mg kg^{-1} h^{-1} (95% confidence limits 2.35–3.37 mg kg^{-1} h^{-1}) and the ED_{95} as 4.98 mg kg^{-1} h^{-1} (4.13–8.8 mg kg^{-1} h^{-1}) when combined with alfentanil in a total i.v. technique. There was a correlation ($r = 0.79$, $P < 0.001$) between the whole blood concentration of propofol at the time of incision and the infusion scheme (fig. 2). The EC_{50} and EC_{95} were

TABLE II. *Mean (SD) patient age and weight, and sex ratio according to group*

	Group				
	1	2	3	4	5
Age (yr)	42.6 (15.3)	40.3 (12.8)	43.5 (14.4)	41.0 (15.8)	41.2 (11.2)
Weight (kg)	69.5 (9.9)	73.7 (11.5)	72.8 (8.7)	72.2 (15.0)	69.3 (9.2)
M.F ratio	8:2	9:1	9:1	6:5	9:1

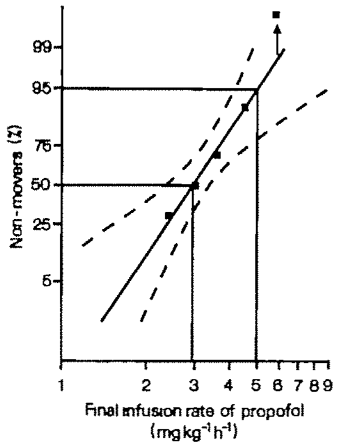

FIG. 1. Log dose probit plot of percentage of patients not moving in response to the initial surgical incision. The percentage of responders in the individual groups are shown as are the 95% confidence limits to the fitted regression line. The arrow beneath the uppermost point indicates that the results from this group add little weight to the determination of the ED_{50} and ED_{95} functions.

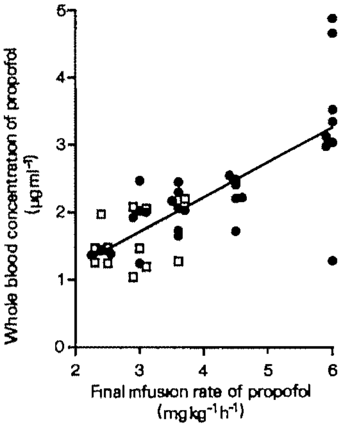

FIG. 2. Whole blood concentration of propofol as a function of infusion rate in 45 patients. □ = Patients who moved; ● = patients who did not move in response to the initial surgical incision. The regression line is given by: $y = 0.34 + 0.58x$ ($r = 0.79$, $P < 0.001$).

1.4 (95% confidence limits 0.62–1.87) $\mu g\ ml^{-1}$ and 4.05 (95% confidence limits 2.78–30.5) $\mu g\ ml^{-1}$, respectively.

All groups showed a significant ($P < 0.001$) decrease in arterial pressure (systolic and diastolic) from the first 1 min onwards, becoming maximal (between −22% and −32% of the preinduction pressures) by 9 min after induction. The pressures were stable thereafter, showing a gradual increase after the onset of surgery. There was no correlation between the degree of hypotension and the infusion rate. All but group 5 had significant decreases in heart rate, maximal by 9 min ($P < 0.05$).

There were no significant changes of arterial pressure or heart rate in response to laryngoscopy and intubation, or in response to the initial surgical incision.

No patient was able to recall any event during anaesthesia or surgery, even at the time of movement in response to the surgical incision. No patient complained of pain on injection of propofol, and there was no evidence of postoperative thrombophlebitis. Episodes of nausea or vomiting were late in the recovery phase and associated with the subsequent administration of other opioids.

The times to extubation, response to command and correct recall of date of birth are shown in table III.

Clonidine subgroup

The eight patients who were given clonidine in addition to their temazepam premedication were not significantly different in age or weight from the other groups. No patients in this group moved in response to the initial surgical incision—a significant decrease by comparison with the number of movers in group 2 who received the same propofol infusion scheme (Fisher exact: $P < 0.05$). The mean whole blood concentration of propofol at incision in this group was slightly less than in the comparison group (group 2), but this was not significant. The median times to extubation (14.5 min), response to command (15.0 min) and recall of birth date (15.5 min) were significantly longer in the patients receiving clonidine, being nearly twice as long as those of group 2 ($P < 0.05$).

DISCUSSION

The concept of minimum infusion rate (MIR) was introduced to define the dose of an i.v. anaesthetic which suppressed movement in response to the initial surgical incision in 50% of patients [21]. Such indices of drug potency as MIR, or the minimum alveolar concentration (MAC) of an inhalation agent, should be determined under conditions of stable blood concentrations of the relevant drug. The manual propofol infusion scheme chosen for this study [14] was designed to achieve a stable blood propofol concentration within 5 min of induction, and to maintain the desired value throughout subsequent anaesthesia and surgery. As the pharmacokinetics of propofol are linear over the range of infusion rates used for surgery [2], proportional changes of the components of the infusion scheme should produce proportional increments in whole blood concentrations of propofol, while still achieving the desired blood concentration quickly, so we used proportional rates of the manual infusion scheme (patient groups 1–5) to determine the dose requirements for propofol when used together with a predetermined alfentanil infusion scheme [13] for total i.v. anaesthesia.

The variability of the blood concentrations of propofol at each infusion rate deserves some comment, especially the apparently wide range of values in the group receiving the highest final infusion rate (6 mg $kg^{-1}\ h^{-1}$). The mean value of this group (3.28 (SD 1.06) $\mu g\ ml^{-1}$) is not sig-

TABLE III. *Recovery characteristics (time from end of infusion) (median (range))*

	Group				
	1	2	3	4	5
Time to extubation (min)	7.0 (4–18)	8.5 (4–14)	10.0 (5–25)	10.0 (5–18)	14.0 (4–23)
Time to response to command (min)	8.5 (4–18)	8.5 (4–16)	10.5 (5–26)	12.0 (6–30)	16.0 (5–29)
Time to recall date of birth (min)	9.0 (4–24)	9.0 (4–18)	12.5 (6–28)	12.0 (6–30)	18.0 (6–32)

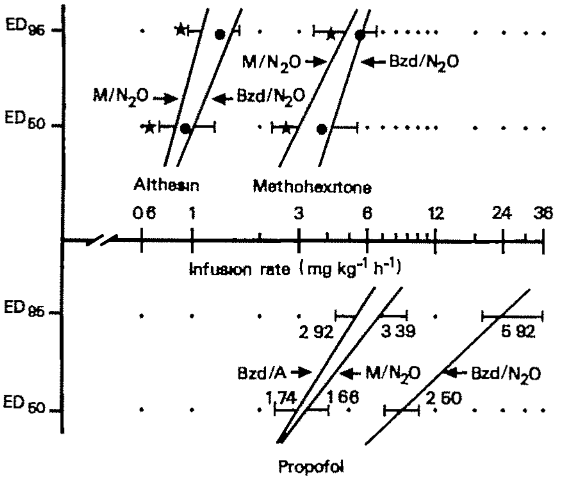

FIG. 3. Summary of the available data on dose–response relationships for propofol (lower half of figure derived from the present study, and from references [10] and [11]) and for Althesin and methohexitone (upper half of figure derived from references [21], [23] and [24]). The labelling of each dose–response curve represents the premedication (M = morphine, Bzd = benzodiazepine) and the anaesthetic supplement (A = alfentanil, N_2O = nitrous oxide) used in the construction of the individual curve. The numerals adjacent to the ED$_{50}$ and ED$_{95}$ points indicate the mean whole blood concentrations of propofol at those infusion rates. ● = Young subgroup; ★ = older subgroup.

nificantly different from the mean of 40 samples (3.42 (0.68) µg ml^{-1}) taken at the same time (20 min) after the start of the infusion in two subsequent studies [14, 22] from our laboratory. The overall mean of the samples taken at the same time in the three different studies is 3.39 (0.75) µg ml^{-1}, which indicates how the three outlying values in figure 2 have an undue influence in the large value for SD in this group of patients. It also indicates that the present data confirm the linear pharmacokinetics within this range of infusion rates [2]. Only when we have sufficient data to perform a population pharmacokinetic study shall we be able to identify specific factors which may influence the variability of the blood concentration of propofol achieved at a given infusion rate.

Several drugs could be used to achieve total i.v. anaesthesia; the choice of the combination of propofol with alfentanil was based on the desirable pharmacokinetic profiles of the two drugs. The purposes of determining dose–response curves are two-fold. First, they provide indices of equipotency of anaesthetics comparable to those for inhalation anaesthetics and allow valid comparisons of other pharmacological effects, such as haemodynamic and ventilatory effects, to be made under comparable conditions. Second, they provide the clinician with reliable dosage schemes which allow an estimate to be made of the smallest doses compatible with adequate anaesthesia.

Figure 3 shows the dose–response curves for infusion of propofol (lower half of figure) under three different conditions. The curve for the present study may be compared with those for propofol used to supplement 67% nitrous oxide in patients premedicated with morphine [10] or benzodiazepines [11]. The dose–response curve in the present study lies just to the left of that for patients receiving nitrous oxide after morphine premedication, and one may deduce that the infusion scheme for alfentanil (derived from [13]) was equivalent to the combined effects of morphine 10 mg and 67% nitrous oxide.

The values for ED$_{50}$ and ED$_{95}$ in the present study are similar to those determined for propofol as a supplement to 67% nitrous oxide anaesthesia in patients premedicated with morphine [10], and those for methohexitone as a supplement to nitrous oxide in morphine-premedicated patients [24]. The slope of the dose–response curve for infusion of propofol in the present study (fig. 3) is steeper than that for the propofol–nitrous oxide–morphine study [10], but slightly flatter than those for methohexitone or Althesin (measured as alphaxalone), also with nitrous oxide in morphine-premedicated patients.

Given the probit regression line, we can extrapolate beyond the ED$_{95}$ to predict the final infusion rate (and its preceding loading dose and step infusion rate changes) which should be sufficient to provide reliable total i.v. anaesthesia. The results achieved in group 5 suggest that this combination of propofol and alfentanil dosage appears to fulfil the majority of requirements for a total i.v. anaesthesia technique [25].

The choice of the alfentanil infusion scheme for this study of total i.v. anaesthesia was based on studies of infusions of alfentanil during nitrous oxide anaesthesia [12, 13, 26]. These studies showed that the 50-µg kg^{-1} loading dose and 50-µg kg^{-1} h^{-1} maintenance infusion rate produced a stable blood concentration within 20 min, provided satisfactory conditions for body surface surgery and allowed a rapid return to an adequate breathing pattern when the infusion rate was decreased to 20 µg kg^{-1} h^{-1}. The infusion rate for alfentanil used in the present study should produce plasma alfentanil concentrations similar to those (167 (28) ng ml^{-1}) observed by O'Connor, Escarpa and Prys-Roberts [13]. However, in view of the variability in plasma concentrations of propofol observed in this study, it is not possible to exclude similar variability in plasma alfentanil concentrations and this has been examined, therefore, in a subsequent study.

The decreases in arterial pressure in the present study were similar to those reported in other studies using propofol to supplement nitrous oxide anaesthesia [3, 4, 14, 15, 27]. The hypotension was associated with a decrease in heart rate of up to 20% over the preinduction rate. In a separate study we have shown that i.v. glycopyrronium 5 $\mu g\ kg^{-1}$, but not atropine 10 $\mu g\ kg^{-1}$, minimized the decrease in arterial pressure in patients anaesthetized with the infusion scheme used for group 5 [9].

It has been known for some time that clonidine decreases anaesthetic requirements for the inhalation agents [16, 17, 28, 29]. To test the hypothesis that clonidine might exert the same effect in reducing the dose requirement for an i.v. anaesthetic, we sought the simplest method to establish the fact, involving the least number of patients. Having defined the response of the group closest to the ED$_{50}$ (group 2), we elected to study the effect of clonidine 0.6 mg added to the premedication in a similar group of patients. Our finding that the number of patients moving at the initial incision was reduced (from five of 10 to none of eight) confirms that clonidine reduces the anaesthetic requirements for propofol. The sedative effect of clonidine may have contributed to the prolonged recovery times seen in this subgroup; indeed, the prolonged recovery more than offset any gain from the reduction in propofol requirement.

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ANALGESIC EFFICACY OF I.M. ALFENTANIL

L. ARENDT-NIELSEN, B. ØBERG AND P. BJERRING

SUMMARY

We have studied the analgesic, respiratory, cardiovascular and sedative effects of alfentanil 30 $\mu g\ kg^{-1}$ i.m. in two experiments in six healthy volunteers. In the first experiment, recordings were made up to 120 min after injection. Thresholds (sensory and pain) and pain-related evoked potentials (amplitude and latency) to cutaneous argon laser stimulation were used for quantitative assessment of onset, efficacy and duration of analgesia. Pain was significantly reduced from 5 to 60 min after injection. The onset phase of analgesia was faster than the recovery phase. In the second experiment, the alfentanil-induced analgesia was antagonized by naloxone 0.4 mg i.v. The reaction time to pain was prolonged significantly 15 min after injection, whereas the latency of the pain-related potential remained constant. No clinically significant changes were observed in respiratory and cardiovascular measurements.

KEY WORDS

Analgesics: alfentanil. Pain: experimental, laser stimulation, evoked potentials

Alfentanil is an opioid analgesic characterized by rapid onset and short duration of action [1, 2] when administered i.v. We have investigated the onset time and the duration of analgesia following i.m. injection. Quantitative evaluation of analgesic efficacy in humans is performed normally in patients receiving other analgesics or medications and with varying degrees of pain. We therefore used a model of experimentally-induced pain and recorded pain-related variables [3, 4] in a group of healthy volunteers.

SUBJECTS AND METHODS

All volunteers were healthy and were receiving no concurrent medication. All gave informed consent according to the Declaration of Helsinki. The study was approved by the local Ethics Committee. Two experiments were performed in the same group of volunteers. In the first, sensory and pain thresholds and evoked potentials were measured to evaluate the onset, efficacy and duration of alfentanil analgesia. The second experiment, 3 weeks later, served as a control. Naloxone, an opioid antagonist, was injected i.v. 17 min after injection of alfentanil, and the effects on thresholds and evoked potentials were determined.

Four females (aged 30–38 yr (mean 32 yr), weights 59–63 kg (mean 60.5 kg)) and two males (aged 26 and 31 yr, weights 73 and 96 kg (mean 84.5 kg)) participated in the study. They were instructed to report any signs of dizziness, drowsiness, nausea, vomiting or other side-effects.

Alfentanil 30 µg/kg body weight was injected into the quadriceps femoris muscle with the subject in the supine position. The subject remained in this position throughout the study.

The electrocardiogram was monitored continuously for 120 min after injection of alfentanil. Arterial pressure and heart rate were measured before and 5, 10, 20 and 40 min after injection. Arterial blood was sampled before and 5, 15 and 40 min after injection. Samples were analysed using an ABL2 blood-gas analyser (Radiometer, Copenhagen).

During the studies, the volunteers rested comfortably and wore goggles to protect the eyes against the laser. To avoid any acoustic interference at the time of the stimulus, earphones and white noise were used. The volunteers were asked

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to keep their eyes open and fix the gaze on the ceiling. The surface skin temperature in the area used for stimulation was monitored by a digital thermometer and maintained at 33±2 °C by a radiant heater. Room temperature was 24±2 °C.

The output from an argon laser (Spectra Physics, model 168, California, U.S.A.) was transmitted to the skin via a single 1-mm quartz fibre. Output power could be adjusted continuously from 50 mW to 3.5 W. The beam comprised light of both 488 nm (blue) and 515 nm (green). The energy distribution at each wave length was 33% and 66%, respectively, and remained constant (±2%) for laser intensities greater than 50 mW. An external power meter (Ophir, Israel) measured the dissipated power leaving the fibre. A continuous, low energy beam (50 mW) was used to visualize the stimulation site. To keep the energy density of the beam low, a 200-ms stimulus duration and a 3-mm laser beam diameter (0.07 cm^2) were used. These stimulus parameters were found previously to be adequate to elicit distinct pain without causing superficial burn lesions [3].

The laser stimuli were applied to the dorsum of the left hand (C7-dermatome) within a target area of 2 cm × 2 cm. The target area was encircled in ink to ensure that the same area was used for consecutive stimulations. Repeated stimuli at an identical point within the area were avoided by dividing the target area into small sectors which were stimulated sequentially.

The sensory and pain thresholds were calculated as the mean of three ascending and three descending series of stimulations. The sensory threshold was defined as warmth, and the pain threshold was defined as a sharp, distinct pinprick [3]. The mean of five subsequent determinations was calculated.

A counter was triggered at the onset of the laser stimulus and stopped by pressing a small thumb switch, using the contralateral (right) hand. Volunteers were instructed to react as soon as pain was perceived [5].

Evoked potentials were recorded from a platinum needle electrode (Disa 25C04), inserted over the vertex with reference to linked ear lobe electrodes. The EEG was amplified, filtered by a second-order filter (0.5–15 Hz) and sampled by a computer [4]. Pain-related potentials evoked over the vertex are large, and 16–24 potentials are sufficient to obtain a good signal-to-noise ratio. The peak-to-peak amplitude and latency of N1 complex with a latency of approximately 300 ms were used for monitoring. The peak-to-peak amplitude was calculated as the mean of P1/N1 and N1/P2 (fig. 1). Initially, two subsequent potentials were recorded, to ensure the validity of the recordings.

Experiment 1. Sensory and pain thresholds were measured before and 2, 5, 10, 15, 25, 30, 45, 60, 90 and 120 min after injection of alfentanil 30 μg kg^{-1} i.m. The evoked potentials were recorded before and 5, 30, 60, 90 and 120 min after injection. Reaction times to pain stimuli were measured before and 15 min after injection.

Experiment 2. In this control investigation, naloxone 0.4 mg was injected i.v. 17 min after injection of alfentanil 30 μg kg^{-1} i.m. The injection time of naloxone was determined from experiment 1, where effective analgesia was obtained 15 min after i.m. alfentanil. The sensory and pain thresholds were measured before and 2, 5, 10 and 15 min after alfentanil, and 2, 5 10, 15 and 30 min after naloxone. The evoked potentials were measured before and 5 and 15 min after alfentanil, and 15 and 45 min after naloxone.

For statistical analysis, Wilcoxon's signed rank test was used. $P < 0.05$ was regarded as significant.

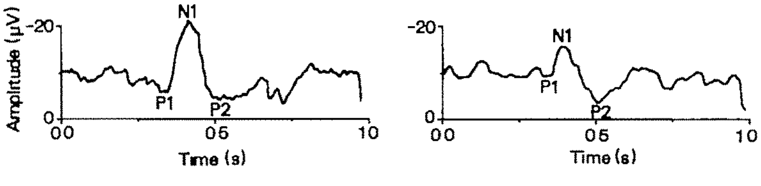

FIG. 1. Examples of pain-related evoked potentials recorded for one volunteer before and 30 min after i.m. alfentanil.

RESULTS

Experiment 1

The pain threshold increased significantly ($P < 0.05$–0.01) from 5 to 60 min after injection of alfentanil, in contrast to the sensory threshold (fig. 2). The maximum increase from 1.14 W to 2.47 W (116%) occurred 15 min after injection. The decay phase of analgesia was substantially longer (30 min) than the onset phase (15 min). None of the volunteers experienced total alleviation of pain from the laser stimulation. After 20 min the volunteers were tested with pinpricks, and all reported that the pain was perceived as less sharp than before analgesia.

Examples of the change in evoked potentials in one subject are shown in figure 1. The amplitudes of the evoked potentials were decreased significantly ($P < 0.01$–0.05) from 5 to 60 min after injection. The maximum decreases in amplitudes occurred 30 min (43%) and 60 min (53%) after injection (table I). The N1 latency of the evoked potential did not differ significantly from the initial recording at any time (table I).

The mean reaction time measured 15 min after injection of alfentanil was 447 (SD 52) ms, which was significantly ($P < 0.05$) longer compared with the reaction time of 406 (58) ms measured before injection.

Experiment 2

The pain threshold was increased significantly ($P < 0.01$) from 1.15 W to 2.3 W (100%) 15 min after injection of alfentanil. Immediately (1–2 min) after injection of naloxone, pain thresholds decreased by 41%, from 2.3 W to 1.35 W (fig. 3). The pain threshold remained constant and did not differ from the control values throughout the rest of the experiment (coefficient of variation of 6.4%). The sensory threshold did not change significantly at any time.

The amplitude of the evoked potential was reduced by 32% ($P < 0.01$) 15 min after injection of alfentanil. This reduction was abolished by naloxone and the recordings 15 min after injection of naloxone did not differ from the initial recordings (table I). The N1 latency of the pain-related complex did not change significantly throughout the study (table I).

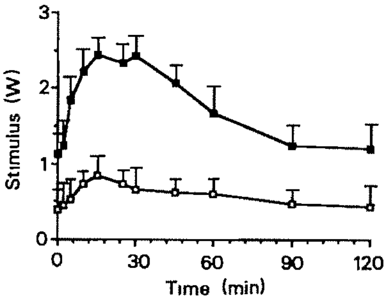

FIG. 2. The effect of i.m. alfentanil 30 μg kg^{-1} on argon laser induced sensory (□) and pain (■) thresholds (mean (SD) for six volunteers). Only pain threshold was significantly ($P < 0.05$–0.01) increased from 5 to 60 min after injection.

TABLE I. *Mean* (SD) *peak-to-peak amplitudes and N1 latencies of the pain-related evoked potential for the six volunteers.* *$P < 0.05$, **$P < 0.01$, *compared with control*

	Time after alfentanil injection (min)					
Experiment 1	0	5	30	60	90	120
Amplitude (μV)	23.9 (5.3)	16.3* (4.3)	13.1** (3.2)	11.2** (3.6)	15.8 (5.7)	17.3 (4.9)
Latency (ms)	350 (33)	362 (13)	357 (22)	352 (31)	350 (13)	366 (18)

	Time after alfentanil (min)			Time after naloxone (min)	
Experiment 2	0	5	15	15	45
Amplitude (μV)	21.1 (4.9)	18.4 (3.8)	15.3* (3.9)	22.4 (5.1)	20.2 (5.8)
Latency (ms)	355 (41)	362 (33)	360 (19)	357 (29)	350 (35)

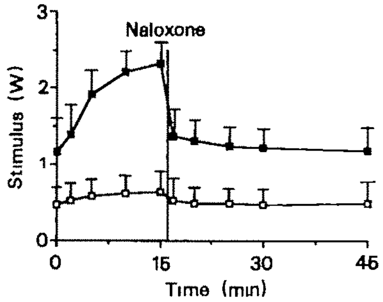

FIG. 3. The effect of i.m. alfentanil 30 µg kg^{-1} on argon laser-induced sensory (□) and pain (■) thresholds (mean (SD) for six volunteers). Only pain threshold was significantly ($P < 0.05$–0.01) increased from 5 to 15 min after injection of alfentanil. Naloxone 0.4 mg i.v. was injected 17 min (vertical bar) after injection of alfentanil. Pain threshold returned to baseline after injection of naloxone.

TABLE II. *Mean (SD) changes in arterial pressure, heart rate and* Pa_{CO_2} *before (0) and after i.m. injection of alfentanil 30 µg kg*$^{-1}$ (n = 6). $^{*}P < 0.05$; $^{**}P < 0.01$, *compared with control*

Time (min)	Arterial pressure (mm Hg)	Heart rate (beat min^{-1})	Pa_{CO_2} (kPa)
0	110 (10)/61 (7)	71 (10)	5.22 (0.46)
5	105 (11)*/58 (5)*	67 (13)	5.80 (0.66)**
10	106 (11)*/59 (9)	67 (12)*	
15			5.73 (0.74)**
20	102 (12)**/58 (9)	67 (11)*	
40	100 (13)**/58 (9)	69 (10)*	5.60 (0.57)**

Mean Pa_{CO_2} increased maximally 5 min after injection of alfentanil. Mean systolic arterial pressure decreased maximally 40 min after alfentanil, but mean diastolic arterial pressure changed little throughout the experiment (table II). Mean heart rate decreased and was least 20 min after injection of alfentanil.

One volunteer complained of severe dizziness (lasting for 10–12 h) and one volunteer experienced moderate nausea. No vomiting occurred. Volunteers reported a reduction in anxiety associated with laser stimulation for the first 30 min after injection.

DISCUSSION

The study showed that laser-induced pain was reduced significantly 5 min after alfentanil 30 µg kg^{-1} i.m. This rapid onset of analgesia might be beneficial for initial treatment of severe pain, as it allows more time for titration of long-acting analgesics. Chauvin and colleagues [6] evaluated the effect of alfentanil 15 µg kg^{-1} i.m. on postoperative pain. They found a rapid onset within the first 1 min and an effect which lasted for 10–60 min. Alfentanil i.v. has been found to alleviate postoperative pain significantly for only 10 min [7].

Evoked potentials to painful dental stimulation have been used to clarify the relation between analgesic effect and plasma concentrations of alfentanil. Chapman and colleagues [8], using a continuous infusion of alfentanil, found that a plasma concentration of 20 ng ml^{-1} reduced the amplitude by 26 %. In the present study using a bolus dose, approximately the same reduction in amplitude was obtained 5 min after i.m. injection.

The amplitude or power of the pain-related evoked potential was found to correlate with the intensity of the pain perceived, and may thus be an objective technique for assessment of acute pain [4]. This potential reflects activity mediated by the thin myelinated Aδ-fibres, and the latency of the complex provides information on conduction delays along the peripheral and central pain pathways [4, 5].

The sensory threshold to argon laser stimulation is perceived as warmth, which is assumed to reflect activity in unmyelinated C-fibres [9]. The pain threshold is perceived as pricking pain, and is assumed to be associated predominantly with activity in thin myelinated Aδ-fibres [10]. Recently, we demonstrated [11] that topical anaesthetics did not have the same effect on sensory and pain thresholds, which indicates that different nerve fibre populations are activated. The present study further substantiates the specificity of the threshold testing technique, because the sensory threshold (perception of warmth) was not affected significantly by alfentanil compared with the changes in pain threshold.

The sedative effect of alfentanil was assessed quantitatively by measuring reaction time to pain. At the time when analgesia was obtained (15 min after injection) the reaction time to pain was increased significantly. This confirms our clinical observation that pain stimulation at that time was not of great concern to the volunteers.

Interestingly, the latency of the evoked potential did not show significant changes, although it has been stated previously that reaction times to painful laser stimuli correlate with the latencies of the laser evoked potentials [5, 12]. In the present study, the conduction velocity along the pain pathways was not reduced, whereas the reaction time from perception of pain to pressing the thumb switch was significantly increased. This indicates a new possibility for studying if various drugs affect predominantly the afferent nociceptive transmission or the motor reaction.

We found that naloxone 0.4 mg antagonized the analgesic effect of i.m. alfentanil, evaluated by both pain threshold and evoked potential. The analgesic effect of alfentanil in rats has been antagonized by naloxone [13], but Chauvin and colleagues [6], in a human study, could not antagonize analgesia with naloxone. Further studies are needed, therefore, to clarify these conflicting findings.

In the present study, alfentanil administered i.m. in a dose sufficient to reduce cutaneous pain did not produce any clinically significant cardiovascular or respiratory side effects. This is in accordance with previous studies, in which use of alfentanil produced stable patterns of haemodynamic variables and few side effects [14]. Our findings supported Chauvin and colleagues [6] who reported that dizziness, nausea and vomiting were less pronounced than after i.m. injection of other opioids.

The development of alfentanil analgesia could not have been evaluated by conventional needle pinprick tests because these are qualitative "on-off" tests, offering no opportunity to evaluate the quantitative development of analgesia. The use of human experimental models for assessment of pain is suited especially for preclinical staging trials of new opioid analgesics, confirming predictions made from animal studies, and studying relative potencies of opioids. The analgesic effect of i.m. alfentanil has not previously been evaluated experimentally in otherwise healthy volunteers.

On the basis of our findings, we suggest that i.m. alfentanil may be used for short painful procedures, for outpatient analgesia, for premedication and for treatment of acute pain.

ACKNOWLEDGEMENT

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EFFECTS OF SUFENTANIL ON MEDIAN NERVE SOMATOSENSORY EVOKED POTENTIALS†

M. A. KIMOVEC, A. KOHT AND T. B. SLOAN

SUMMARY

We have studied the effects of a single i.v. dose of sufentanil 5 $\mu g\ kg^{-1}$ in combination with pancuronium on the median nerve short latency somatosensory evoked potentials (SSEP) in 15 unpremedicated patients undergoing thoracic or lumbar spinal surgery. The latency and amplitude of the SSEP response over the second cervical vertebra (SC) and sensory cortex (P17, N20, P25), heart rate and arterial pressure were recorded for 30 min after the injection of sufentanil. A significant increase in mean latency occurred for N20 ($P < 0.003$) and P25 ($P < 0.002$) within 2 min, but the absolute increase in latency was small. The mean amplitudes of all peaks decreased to 60% (SC), 70% (P17), 60% (N20) ($P < 0.012$) and 45% (P25) of the baseline value within 7 min. The results suggest that the major change in median nerve SSEP produced by this dose of sufentanil is a reduction in amplitude, and that major changes in latency after sufentanil and pancuronium are probably caused by other influences.

KEY WORDS

Analgesics, opioid: sufentanil. Monitoring: somatosensory evoked potentials

Evoked potential monitoring is an accepted technique for objective measurement of function in the sensory spinal tracts and has been used to monitor spinal integrity during surgery. Many factors influence the ability to monitor the somatosensory evoked potentials (SSEP), including anaesthetic agents, physiological variables, technical problems and surgery. Veilleux, Daube and Cucchiara reported reductions in ulnar nerve and tibial nerve cortical evoked potential amplitudes shortly after induction of anaesthesia in 12% of their patients [1]. Drug-induced changes in SSEP must be determined to permit their discrimination from adverse effects of patient positioning for surgery.

As inhalation agents appear to affect monitoring ability more than opioids [2, 3], an opioid-based anaesthetic technique is often used. Sufentanil, an opioid agonist selective for the mu receptor [4, 5], has a high therapeutic index [6] and is used widely in a dose of 5 $\mu g\ kg^{-1}$ [7–9].

The present study was undertaken to determine the effects of a single bolus of sufentanil 5 $\mu g\ kg^{-1}$ in combination with pancuronium on the short latency median nerve SSEP in humans.

PATIENTS AND METHODS

Fifteen ASA physical status I and II patients undergoing thoracic or lumbar spinal surgery with SSEP monitoring gave written consent to participate in the study, which was approved by the institutional review boards. Patients with neurological abnormalities in the median nerve pathway or intracranial pathology were excluded.

Patients came to the operating room without premedication. An i.v. catheter was inserted and the overnight fluid deficit replaced with 5% glucose in lactated Ringer's solution. Routine monitoring included precordial stethoscope, spirometer, continuous electrocardiogram,

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automated oscillotonometry, temperature and capnograph.

After skin abrasion, disc recording electrodes with electrode paste were affixed with collodion at Fz (reference), the inion (SC), and 2 cm posterior to C3 and C4 (International 10–20 System). A silver–silver chloride ground electrode was placed on the shoulder. All electrode impedances were less than 3000 Ω and electrode pairs matched within 1000 Ω. Median nerve SSEP were obtained using stimulation at the wrist with a bipolar bar electrode and electrode gel. Constant current stimulation used 300-µs square wave impulses at 5.7–8.7 Hz, 1 mA greater than that sufficient to produce a motor response.

For each averaged waveform, 250 artefact-free responses were acquired using a Pathfinder II or CA-1000/DC-2000 signal averager (Nicolet Biomedical Instruments, Madison, Wisconsin), with bandpass filter settings of 5–250 Hz (60 Hz notch filter was not used) and an analysis window of 50 ms. All acquired data were stored on magnetic discs for later analysis.

After two satisfactory baseline recordings were obtained, pancuronium 0.02 mg kg^{-1} was given i.v., followed by sufentanil 5 µg kg^{-1} over 30 s. The SSEP, arterial pressure (AP) and heart rate (HR) were recorded at 1-min intervals for 9 min, and then every 3 min until 30 min after injection. Additional pancuronium (to a total of 0.12 mg kg^{-1}) was given as required. Ventilation was assisted manually as necessary using a facemask with 40 % oxygen in air to maintain end-tidal $P\text{CO}_2$ at 4.7–6 kPa. All patients were normothermic at the end of the study.

Latency and amplitude values were calculated after the study by recall of stored averages. Post-stimulus latency of the major cervical negative wave (SC) (approximately 15 ms) and the latencies of the primary cortical response waves (P17, 17 ms; N20, 20 ms; and P25, 25 ms) were recorded. Conduction times were calculated as the time intervals between various peaks. Amplitude was measured as the voltage from the peak of interest to the following peak of opposite polarity (e.g., cortical N20 amplitude was measured from N20 to P25).

SSEP latencies, conduction times, amplitudes and physiological variables (AP and HR) were compared using Friedman two-way analysis of variance. Differences were confirmed by Wilcoxon matched pairs signed ranks test. Statistical significance was assumed when $P < 0.05$.

RESULTS

We studied nine women and six men: mean age 35 yr (range 24–55 yr), height 169 cm (range 152–185 cm) and weight 73 kg (range 55–115 kg).

There was no difficulty obtaining the post-stimulus latencies immediately after the sufentanil bolus in any patient. The median nerve SSEP obtained from one patient are shown in figure 1, and mean (SD) values for group data acquired during the entire study period are presented in table I. A statistically significant increase in latency occurred in the cortical N20 ($P < 0.003$) and the cortical P25 ($P < 0.002$). Wilcoxon analysis demonstrated a significant difference between time 0 and later times, confirming that the increase occurred immediately after injection (1–2 min). The absolute latency increase was, however, small. Changes in the latencies of the cervical and cortical P17 were also small and not statistically significant.

Analysis of the interwave latencies (conduction times) revealed significant differences between SC and cortical N20 ($P < 0.002$) and between SC and cortical P25 ($P < 0.003$). Again, the major changes

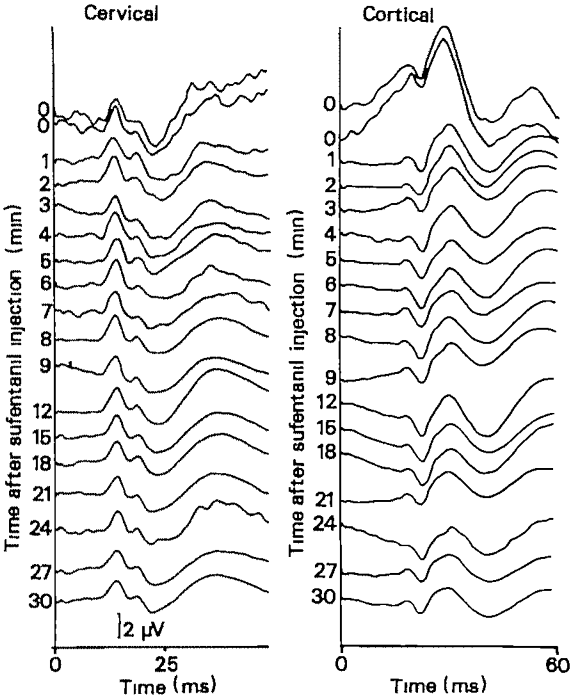

FIG. 1. Changes in median nerve cervical and cortical SSEP recordings with time in one patient after sufentanil 5 µg kg^{-1}. Two baseline recordings at time zero are shown.

TABLE I. *SSEP and cardiovascular data (mean (SD)) at selected times after administration of sufentanil and pancuronium. SC = SSEP response over second cervical vertebra; P17, N20 and P25 = SSEP response over sensory cortex. HR = Heart rate; SAP and DAP = systolic and diastolic arterial pressures.* *P < *0.05 compared with baseline*

	Baseline	1 min	2 min	6 min	12 min	30 min
Latency						
SC	14.9 (1.1)	14.8 (1.2)	14.6 (0.9)	14.9 (1.1)	15.0 (1.3)	15.0 (1.3)
P17	17.0 (1.0)	17.1 (1.2)	17.3 (1.3)	17.3 (1.2)	17.3 (1.2)	17.4 (1.4)
N20	20.2 (1.3)	21.1 (1.8)*	21.3 (1.8)*	21.4 (1.8)*	21.4 (1.4)*	21.3 (1.4)*
P25	25.2 (2.5)	26.2 (3.0)*	26.7 (2.9)*	26.7 (2.9)*	26.6 (2.7)*	26.6 (2.8)*
Central conduction time						
SC–N20	5.3 (1.3)	6.2 (1.4)*	6.1 (1.4)*	6.4 (1.3)*	6.4 (1.1)*	6.2 (1.2)*
Amplitude						
SC	2.7 (1.6)	1.6 (0.8)	1.4 (1.0)	1.5 (0.8)	1.8 (1.6)	1.5 (1.0)
P17	1.6 (1.2)	1.0 (0.8)	1.1 (0.9)	1.0 (0.9)	1.2 (0.8)	1.1 (1.0)
N20	3.6 (2.5)	2.2 (1.7)*	2.1 (1.6)*	2.3 (1.5)*	2.1 (1.4)*	2.3 (1.9)*
P25	4.4 (2.7)	2.3 (1.8)	2.3 (1.8)	2.1 (2.3)	1.9 (1.5)	2.2 (1.8)
Physiological variables						
HR (beat min^{-1})	84 (14)	99 (23)*	98 (19)*	89 (2)*	98 (25)*	91 (35)*
SAP (mm Hg)	135 (16)	134 (19)	137 (18)	123 (19)*	132 (20)	134 (17)
DAP (mm Hg)	76 (14)	78 (12)	70 (31)	80 (14)	79 (14)	73 (13)

occurred between the baseline and later times, but were small.

Baseline amplitudes varied between patients and were in the ranges 0.21–6.96 μV (SC), 0.14–4.64 μV (P17), 0.71–11.3 μV (N20) and 0.92–8.78 μV (P25). The amplitudes of all peaks consistently decreased rapidly (within the first 1 min) and reached a stable value by 6–7 min. The final values for the amplitudes were approximately 60 % (SC), 70 % (P17), 60 % (N20) and 45 % (P25) of the baseline value. The change in N20 amplitude was statistically significant ($P < 0.012$).

AP and HR changed little during the study. A transient reduction in systolic arterial pressure with maximal change at 6 min was statistically ($P < 0.0001$), but not clinically, significant. A sustained increase in HR occurred which also was statistically ($P < 0.032$), but not clinically, significant.

DISCUSSION

The anaesthetic technique used during evoked potential monitoring should be chosen to allow adequate SSEP signal acquisition. Often, several drugs are used during induction of anaesthesia, each contributing an effect on the SSEP. These effects and their time course should be noted after induction, to permit detection of changes resulting from positioning, temperature, ischaemia or surgery.

The effects of sufentanil on SSEP have not been described previously. Several studies have examined the effect of fentanyl on evoked potentials. McPherson, Sell and Traystman noted an increase in N20 and P23 latencies and a decrease in amplitude after a bolus dose of fentanyl 25 μg kg^{-1} [10], but they did not specify the time of measurement. These changes are similar to those found with sufentanil in the present study. Loughnan and colleagues measured the median nerve SSEP after a bolus dose of fentanyl 200 μg and noted a downward trend in amplitude [11]. After high-dose fentanyl (53.2 μg kg^{-1}), Schubert and co-workers noted an increase in the cortical N20 latency and a decrease in cortical amplitude. However, their patients received diazepam and morphine premedication before the study [12]. Although these studies with fentanyl did not examine closely the early time course after injection, the minimal changes in latency with decreases in amplitude were similar to the changes seen with sufentanil in this study. This similarity in action has been seen in EEG studies [13–15].

Pharmacokinetic studies suggest that sufentanil should have a rapid onset of action in the central nervous system with a peak effect at about 5 min [8]. Sufentanil has a high tissue affinity with rapid, extensive uptake into tissues which may be related to its lipophilic nature. Cooke and Scott used the EEG as a continuous quantitative measure of sufentanil activity and showed that a 125-μg bolus caused a 50 % reduction of the spectral edge within a mean of 60 s [13]. Bovill and colleagues also found EEG changes within 30–60 s after a bolus of sufentanil 15 µg kg^{-1}, which remained stable for 5 min [15]. In the present study, the SSEP changes also occurred rapidly and were significantly different from baseline by 1 min, the first time of recording after the drug was given.

Pancuronium was used in this study to permit maintenance of an adequate airway. Neuromuscular blocking drugs have no effect on SSEP latency and amplitude [16–18] and the SSEP changes in this study are therefore most likely to have been produced by sufentanil. The changes in HR and AR, however, were probably caused by the combination of both drugs. The minimal changes seen suggest that the combination of sufentanil and pancuronium may be acceptable for induction of anaesthesia.

Two patients had recall immediately after administration of sufentanil. One complained of an inability to breathe and swallow and another remembered a hand brushing over the eyes. They were subsequently amnesic for the remainder of the study. During pilot studies, two of three patients given sufentanil 2.5 µg kg^{-1} had recall, and this dose was not used again. No patient was given premedication which could alter the SSEP but, after the study, all patients received supplementation with diazepam, hyoscine and isoflurane for surgery. No intraoperative awareness occurred. As an opioid-based technique does not guarantee amnesia [19], sufentanil should be supplemented by other agents.

In conclusion, sufentanil in a dose of 5 µg kg^{-1} may be used during surgery where SSEP monitoring is planned. Sufentanil affected the short latency median nerve SSEP primarily by reduction in amplitude, with minimal changes in latency. Stable SSEP recordings were obtained rapidly and monitored easily. Any major change in latency may therefore be of neurological significance.

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EFFECT OF SURGERY ON SENSORY THRESHOLD AND SOMATOSENSORY EVOKED POTENTIALS AFTER SKIN STIMULATION

C. LUND, O. B. HANSEN AND H. KEHLET

SUMMARY

*We have studied the effect of surgical injury on cutaneous sensitivity and somatosensory evoked potentials (SSEP) to dermatomal electrical stimulation in 10 patients undergoing hysterectomy. Forty-eight hours after surgery, sensory threshold increased from 2.2 (*SEM *0.3) mA to 4.4 (1.1) mA (*$P < 0.01$*) and SSEP amplitudes in P1, N1, P2 and the peak-to-peak amplitudes decreased (*$P < 0.05$*). Latency was prolonged only in the N3 component (*$P < 0.05$*). No changes were seen in threshold and SSEP in a control group studied over the same interval. The results suggest that surgical injury activates antinociceptive modulatory systems.*

KEY WORDS

Brain· somatosensory evoked potentials. Surgery. gynaecological.

The effect of surgical injury on sensory threshold in man is unknown, but in experimental studies a post-injury decrease in sensory threshold has been described, mediated probably by an increase in peripheral and central nervous system excitability [1–5].

Electrical stimulation of the skin has been used in the assessment of cutaneous sensibility [6], and measurement of somatosensory evoked potentials (SSEP) is an accepted method for objective assessment of the integrity of sensory pathways and has been used previously in pain research [7–10].

The aim of this study was to assess the effect of surgery on sensory threshold and on cortical SSEP following cutaneous electrical stimulation.

PATIENTS AND METHODS

We studied 10 women undergoing abdominal hysterectomy through an infraumbilical incision in the T12–L1 dermatomes. Mean age was 38 yr (range 22–53 yr). None had symptoms, signs or a history of neuromuscular disease. Informed consent was obtained from all patients.

Ten non-operated control subjects (mean age 32 yr, range 20–36 yr) were investigated using the same procedure as for the surgical patients (see below).

Electrical stimuli of 0.2 ms duration were applied via a 7 × 30 bipolar surface electrode (DANTEC/DISA 13 L 22, Copenhagen, Denmark) at a rate of 1.5 Hz. The cutaneous sensory nerves of the L1 dermatome were stimulated at the anterior superior iliac spine, with an intensity of four times the preoperative sensory threshold (TS). TS was defined as the mid point between the stimulus intensity for just detectable perception and loss of perception of stimulation. Direct stimulation of muscles in the area was avoided and stimulation always resulted in tolerable pain. The stimulating electrode was placed at the same point for both measurements, which took place on the day before operation and 48 h after operation.

Cortical activity was recorded via platinum needle electrodes (DANTEC/DISA 25 C 04) at the midline of the scalp, 2 cm posterior and 5 cm anterior (reference) to the vertex location C_z of the International 10–20 system for EEG recording. One thousand responses were averaged for each

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measurement using a DANTEC/DISA Neuromatic 2000 neuromyograph. The amplifier had a bandpass (−3 dB) of 0.5–1000 Hz; the analysis time was 500 ms. The latency of the onset (0) and the first positive (P1–P3) and negative (N1–N3) peaks and the peak-to-peak amplitudes were measured.

A visual analogue pain score (VAS) was made before and 48 h after surgery just before the recordings of SSEP and TS.

Diazepam 0.2 mg kg^{-1} was given orally as premedication 1 h before surgery. Anaesthesia was induced with thiopentone 5 mg kg^{-1} i.v. and fentanyl 7 µg kg^{-1}; intubation of the trachea was facilitated with suxamethonium 100 mg i.v. after precurarization with pancuronium 0.01 mg kg^{-1} i.v. Anaesthesia was maintained with halothane in nitrous oxide and oxygen. Neuromuscular block was obtained with pancuronium if indicated clinically. Morphine 0.1 mg kg^{-1} i.v. was given every 4–6 h after operation for pain relief. Analgesic drugs were not given for at least 12 h before postoperative SSEP measurements.

Statistics

Changes in SSEP were assessed by Student's *t* test for paired data; $P < 0.05$ was considered statistically significant.

RESULTS

Absolute and peak-to-peak amplitudes decreased after operation; these changes were statistically significant for P1, N1 and P2 (table I). There was a significant increase in latency in the N3-component ($P < 0.05$), while all other latencies remained unchanged (table I).

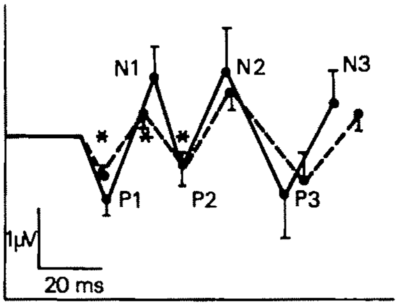

FIG. 1. Mean (SEM) cortical SSEP before (——) and 48 h after (----) surgery following stimulation of the L1 dermatome. $n = 10$. Change in latency is not shown. $*P < 0.05$.

TABLE I. *Effect of surgery on latency and amplitude of the early components of SSEP before and 48 h after surgery following stimulation of the L1 dermatome (mean (SEM)).* $*P < 0.05$ *compared with preoperative value*

	Before op.	After op.
Latency (ms)		
Onset	23 (1)	23 (2)
P1	31 (1)	30 (2)
N1	46 (2)	43 (2)
P2	55 (2)	55 (3)
N2	68 (2)	70 (2)
P3	87 (2)	90 (3)
N3	101 (3)	110 (3)*
Amplitude (µV)		
P1	1.0 (0.2)	0.6 (0.1)*
N1	1.9 (0.4)	1.0 (0.2)*
P2	1.4 (0.3)	0.9 (0.2)*
N2	1.5 (0.6)	1.2 (0 3)
P3	1.9 (0.7)	1.4 (0.4)
N3	1.5 (0.4)	1.1 (0.2)
Peak-to-peak	2.5 (0.6)	1.6 (0.3)*

Figure 1 shows the mean SSEP before and after operation.

TS increased after operation in nine of 10 patients ($P < 0.01$). Mean TS was 2.2 (SEM 0.3) mA before surgery and 4.4 (1.1) mA after surgery (table I). The mean pain score was 0.4±0.3 before surgery and 4.7±1.4 ($P < 0.01$) before the postoperative recording (table II). There was no correlation between changes in TS and increase in pain score.

In the control group there were no differences in amplitudes and latencies or in TS between the first and the second recordings (table III).

TABLE II. *Effect of surgery on sensory threshold (TS) and visual analogue pain score (VAS) of the 10 patients before and 48 h after surgery.* $*P < 0.01$ *compared with value before operation*

Patient No.	TS (mA)		VAS	
	Before	After	Before	After
1	2.0	2.6	—	—
2	1.5	3.5	0	0
3	3.1	3.6	2	9
4	1.0	2.1	0	4
5	2.3	2.7	0	7
6	3.5	14.0	2	4
7	2.0	5.6	0	10
8	4.0	4.0	0	0
9	2.0	2.5	0	3
10	0.9	3.2	0	5
Mean (SEM)	2.2 (0.3)	4.4 (1.1)*	0.4 (0.3)	4.7 (1.4)*

TABLE III. *Latency and amplitude of cortical SSEP at two recordings 48 h apart in 10 control subjects following stimulation of the S1, T10 and L1 dermatomes (mean* (SEM)). *$^*P < 0.05$

	S1 dermatome		T10 dermatome		L1 dermatome	
	Recording 1	Recording 2	Recording 1	Recording 2	Recording 1	Recording 2
Latency (ms)						
Onset	38 (5)	38 (5)	32 (5)	31 (4)	25 (1)	25 (2)
P1	44 (5)	44 (5)	38 (4)	37 (4)	32 (1)	35 (2)
N1	55 (5)	55 (5)	48 (4)	49 (4)	44 (1)	45 (1)
P2	71 (5)	70 (5)	62 (6)	61 (4)	58 (3)	59 (3)
N2	89 (8)	86 (7)	77 (5)	78 (5)	73 (5)	76 (5)
P3	107 (8)	106 (7)	90 (7)	89 (7)	95 (7)	95 (5)
N3	131 (9)	133 (9)	111 (6)	108 (8)	113 (21)	126 (15)
Amplitude (μV)						
P1	2.2 (0.6)	1.9 (0.5)	0.5 (0.1)	0.5 (0.0)	1.2 (0.2)	1.5 (0.2)
N1	3.8 (1.4)	3.7 (1.2)	1.0 (0.2)	1.0 (0.2)	1.9 (0.3)	2.1 (0.3)
P2	3.4 (1.2)	2.9 (1.2)	1.1 (0.2)	1.1 (0.2)	1.4 (0.3)	1.7 (0.4)
N2	2.0 (0.4)	2.0 (0.5)	1.0 (0.2)	1.1 (0.2)	1.5 (0.3)	2.2 (0.3)
P3	3.2 (0.7)	3.4 (0.6)	0.7 (0.2)	0.9 (0.2)	2.2 (0.3)	2.6 (0.4)
N3	3.1 (0.7)	3.3 (0.7)	1.1 (0.2)	0.9 (0.2)	1.6 (0.3)	1.8 (0.6)
Peak-to-peak	5.4 (1.2)	5.2 (1.1)	1.5 (0.2)	1.4 (0.2)	2.7 (0.4)	3.2 (0.4)*
Stimulus intensity	10.1 (0.8)	10.1 (0.8)	13.1 (1.3)	13.1 (1.3)	13.5 (1.8)	13.5 (1.8)
Sensory threshold (mA)	2.4 (0.2)	2.2 (0.2)	3.2 (0.3)	3.3 (0.3)	3.3 (0.5)	3.0 (0.3)

DISCUSSION

This study has demonstrated a pronounced increase in sensory threshold after operation as assessed by electrical stimulation. In contrast, previous studies have shown a post-injury hypersensitivity demonstrated by a decrease in TS [3–5]. The hypersensitivity has been attributed to an injury-induced increase in receptive fields in the dorsal horn [1, 2] and "sensitization" of the peripheral nociceptors. The difference is unlikely to be a result of chance variation, as the measurement of TS has been shown to be highly reproducible [6], which was confirmed by our control subjects.

It is also unlikely that the morphine administered to the surgical patients 12 h previously would have influenced SSEP, as both intraoperative [11] and extradural administration [12] have no effect on SSEP.

Changes in TS and SSEP have not been studied in surgical patients, but both an increase [13] and no change [14] in pain threshold have been demonstrated during labour.

The perception of pain can be suppressed or modified by stress [15, 16] and clinical studies have shown that noxious peripheral stimuli can induce analgesia [16, 17]. This mechanism is probably the activation of descending inhibitory systems from the brain to the dorsal horn. The pharmacology of the descending inhibitory pathways has not been evaluated completely, although several monoamines (serotonin, noradrenaline, dopamine), enkephalin, substance P and cholecystokinin may be involved [18]. A study in patients with sciatic nerve pain demonstrated a decrease in subjective pain induced by electrical stimulation of the sural nerve when performing painful manipulation on the affected side [19].

These studies support our finding of an increase in postoperative TS in patients suffering from pain. Further support comes from the diffuse noxious inhibitory controlling system theory of LeBars and co-workers [20]. They propose that wide dynamic range (WDR) neurones from one area of the body are inhibited by application of stimuli to the same or other areas. Thus the more intense and noxious stimuli from the surgical area in our patients, corresponding to T11–L1 dermatomes, may have inhibited afferent transmission through WDR neurones in the dorsal horn corresponding to the L1 segment.

Our results in surgical patients are in accord with previous findings of a decrease in SSEP components during ischaemic pain in normal subjects [21]. The decrease in SSEP amplitudes suggests modified transmission of stimuli from the stimulation area to the brain. The contribution of the various fibre types to the SSEP has been discussed [1], but no final conclusion has emerged. Presumably, activation of fast conducting fibres (e.g. Aβ, Aδ) is responsible for early responses with latencies $\leqslant$ 500 ms, while C-fibre mediated responses have latencies of 1.5–2.0 s [7].

There is a marked difference between the results of our clinical study and previous experimental studies. Generally, hypersensitivity and lowering of TS have been demonstrated following injury, in contrast with our finding of an increase in TS. However, an explanation for this discrepancy may be that the animal studies were performed on decerebrate animals, thereby preventing descending inhibitory pathways [18] from exerting a modulatory effect on the incoming stimuli. Thus, in the intact organism, recording from the brain would register a decrease in sensory input to the brain as assessed by a decrease in SSEP and an increase in TS. In addition, the animal studies recorded from peripheral afferent nerve fibres [1, 4, 5] or within the spinal cord in the dorsal horn cells [3, 22], thereby missing a possible inhibitory effect from supraspinal centres.

In conclusion, we have shown that surgical trauma increases the sensory threshold as assessed by electrical dermatomal stimulation within the surgical area. Furthermore, surgical trauma decreases the amplitude of early SSEP, but leaves latency largely unchanged.

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PHARMACOKINETICS OF PROPOFOL INFUSIONS IN PATIENTS WITH CIRRHOSIS

F. SERVIN, I. D. COCKSHOTT, R. FARINOTTI, J. P. HABERER, C. WINCKLER AND J. M. DESMONTS

SUMMARY

We have compared the pharmacokinetics of propofol as an infusion in 10 control and 10 patients with cirrhosis. Anaesthesia was induced within 3–4 min during administration of an infusion of propofol 21 mg kg^{-1} h^{-1}*. After 5 min, the infusion was decreased in a stepwise manner to 12 mg* kg^{-1} h^{-1} *and subsequently 6 mg* kg^{-1} h^{-1}*. The mean recovery time after discontinuation of the infusion was significantly longer in the cirrhotic group; however, when patients opened their eyes, blood concentrations of propofol were similar in both groups (1 µg* ml^{-1}*). Pharmacokinetic analysis was performed from the beginning of infusion to 8 h after termination. Total body clearance was not reduced significantly in cirrhotic (1.56 (SD 0.48) litre* min^{-1}*) compared with control (1.75 (0.32) litre* min^{-1}*) patients. The volume of distribution at steady state was significantly greater in patients with cirrhosis than in control patients (202 (82) litre vs 121 (49) litre). However, this difference did not change terminal elimination half-life. The pharmacokinetics of propofol given by infusion to maintain general anaesthesia were not affected markedly by moderate cirrhosis.*

KEY WORDS

Anaesthetics, intravenous propofol. Anaesthetic techniques, intravenous infusion. Liver. cirrhosis. Pharmacokinetics: propofol.

Propofol is used to maintain anaesthesia by continuous infusion. Although distributed extensively into tissues, the drug is known to be cleared rapidly and linear pharmacokinetics have been observed with infusion to healthy patients [1]. The disposition of propofol was similar after single bolus injection and infusion for maintenance of anaesthesia. Propofol is cleared from the body primarily by metabolism [2], but no significant differences in disposition were observed after single bolus administration to patients with cirrhosis and control patients [3]. However, this finding cannot be extrapolated confidently to infusions, as propofol concentrations were only transiently within the range required to maintain anaesthesia.

The aim of this study was to compare the pharmacokinetics of propofol administered as an infusion for maintenance of anaesthesia in control patients and others with cirrhosis.

PATIENTS AND METHODS

The pharmacokinetics of propofol in 10 patients with cirrhosis aged 37–64 yr (mean 53.5 (SD 8.8) yr) and weighing 51–80 kg (64.7 (9.0) kg) were compared with those for patients with normal renal and hepatic function (24–56 yr (mean 41.9 (SD 11.7) yr) and 50–96 kg (65.6 (14.9) kg)). All patients were undergoing elective surgical procedures and gave informed consent. For all cirrhotic patients, cirrhosis had been established

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TABLE I. *Characteristics and liver function tests of patients with cirrhosis. SGPT = Serum glutamic pyruvic transaminase (normal value < 30 iu ml^{-1}). Normal values : * < 20 µmol litre^{-1}; † < 180 iu ml^{-1}*

Patient No	Surgical procedure	Age (yr)	Sex	Child's classification	Plasma albumin (g litre^{-1})	SGPT (iu ml^{-1})	Serum bilirubin* (µmol litre^{-1})	Prothrombin time (% of normal)	Serum alkaline phosphatase† (iu ml^{-1})
1	Hip replacement	64	M	B	34	13	170	100	235
2	Wound dehiscence	62	F	B	29	20	20	81	122
3	Colectomy	55	M	B	29	35	28	61	210
4	Laparotomy	58	M	A	48	25	14	100	66
5	Peritoneo-jugular shunt	60	F	A	34	23	39	75	91
6	Splenorenal shunt	57	M	A	43	39	3	78	108
7	Portocaval shunt	42	F	B	32	21	21	66	197
8	Portocaval shunt	37	F	B	29	41	23	67	286
9	Portocaval shunt	48	M	A	29	139	21	78	104
10	Portocaval shunt	52	M	A	27	78	26	64	84

by liver biopsy; all these subjects had suffered previously from clinical decompensation. None of the patients with cirrhosis had ascites or encephalopathy at the time of the study and none had ingested alcohol for at least 2 weeks before the study. The degree of liver dysfunction, as estimated from liver function tests, was moderate and compatible (group A or B according to Child's classification) with elective surgery (table I).

All patients were premedicated orally with diazepam 10 mg and atropine 1 mg 1 h before anaesthesia. An i.v. cannula was placed in a large forearm vein for injection of propofol. Following infiltration with lignocaine, a cannula was inserted in an artery in the contralateral arm for monitoring arterial pressure and collection of blood samples for pharmacokinetic analysis.

Anaesthesia was induced and maintained using a stepwise infusion regimen of propofol 21 mg kg^{-1} h^{-1} for 5 min, 12 mg kg^{-1} h^{-1} for 10 min and 6 mg kg^{-1} h^{-1} for the rest of the procedure, which lasted for a minimum of 2 h. When the patient lost consciousness, muscle relaxation was produced with vecuronium 0.1 mg kg^{-1} and the trachea was intubated. Small incremental doses of fentanyl (50 µg) were given i.v. as required throughout the procedure. The patient's lungs were ventilated to normocapnia with a mixture of 66% nitrous oxide in oxygen. At the end of the procedure, the propofol infusion and nitrous oxide administration were stopped simultaneously. The time from the beginning of infusion to the loss of consciousness, time to opening eyes on verbal command after stopping the infusion, the duration of the infusion and the total amount of propofol infused were recorded.

For pharmacokinetic analysis, 5-ml arterial blood samples were collected before infusion of propofol and at 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 15, 20, 25, 30, 40, 50, 60, 75, 90, 105 and 120 min thereafter. For infusions continuing beyond 120 min, additional samples were obtained every 15 min. A sample was taken as the infusion was stopped, and further samples were collected 2, 4, 6, 8, 10, 20, 40, 60, 90, 120, 180, 240, 300, 360, 420 and 480 min after the end of the infusion. An additional sample was drawn when the patient opened the eyes to verbal command. After thorough mixing, the samples were cooled immediately to 4 °C and stored at that temperature until subsequent analysis. Whole blood concentrations of propofol were measured by high pressure liquid chromatography [4].

Two- and three-exponential models of the following form, derived from Colburn [5], were fitted to the data using the extended least squares curve-fitting program Elsfit version 3.1 [6]:

$$c_t = 3.5\star \sum_{i=1}^{2 \text{ or } 3} c_i\star(1-\mathrm{e}^{-\lambda_i \star T_1})\star \mathrm{e}^{-\lambda_i \star (t-5)}$$

$$+2.0\star \sum_{i=1}^{2 \text{ or } 3} c_i\star(1-\mathrm{e}^{-\lambda_i \star T_2})\star \mathrm{e}^{-\lambda_i \star (t-15)}$$

$$+1.0\star \sum_{i=1}^{2 \text{ or } 3} c_i\star(1-\mathrm{e}^{-\lambda_i \star T_3})\star \mathrm{e}^{-\lambda_i \star (t-T)}$$

where $T = T_1 + T_2 + T_3$; T_1, T_2 and T_3 are the times from the start of each infusion to maximum values; t is the time from the start of the infusion; c_i are fitted coefficients; and 3.5, 2.0 and 1.0 are the ratios of the three infusion rates to the terminal infusion rate (6 mg kg^{-1} h^{-1}).

The goodness of fit of the two- and three-exponential models was compared using the Schwarz criterion [7] and by visual assessment of the residuals of the observed values from the fitted curve.

The following parameters were derived from the fitted model:

steady state propofol concentration (C^{ss})

$$= \sum_{i=1}^{2 \text{ or } 3} c_i \tag{1}$$

total body clearance (Cl)

$$= \text{terminal infusion rate}/C^{ss} \tag{2}$$

volume of the central compartment (V)

$$= \text{total dose}/\sum_{i=1}^{2 \text{ or } 3} c_i \text{ corr.} \tag{3}$$

where c_i corr. are the fitted coefficients corrected for the infusion duration using the method described by Loo and Riegelman [8].

Model independent parameter estimates were derived as follows:

$$Cl = \text{total dose}/\text{AUC}_\infty$$

where AUC_∞ is the area under the propofol concentration curve extrapolated to infinity, calculated using the trapezoidal approximation:

$$\text{mean residence time (MRT)} = \text{AUMC}_\infty/\text{AUC}_\infty$$

where AUMC_∞ is the area under the first moment of the propofol concentration curve extrapolated to infinity, calculated using the trapezoidal approximation:

apparent volume of distribution at steady state (V^{ss}) $= [\text{total dose}/\text{AUC}_\infty] \times [(\text{AUMC}_\infty/\text{AUC}_\infty) - (T/2)]$

Statistical analysis was by Wilcoxon rank sum test for between-group comparisons of pharmacokinetic data and t test for between-group comparisons of measured data; $P < 0.05$ was considered significant. Values are expressed as mean (SD).

RESULTS

Five patients with cirrhosis were classified as group A according to the Child's classification [9], and five were classified as group B (table I). Plasma concentration of albumin was less than 30 g litre^{-1} in five patients. Hepatocellular insufficiency was moderate in all subjects; they all had a prothrombin time > 60% normal. Five patients underwent portocaval shunt; surgical procedures undergone by the control patients were: colectomy (two), cholecystectomy with repair of hiatus hernia (one), selective vagotomy (one), hysterectomy (one), recurrent bilateral hernia repair (one), femoral pseudarthrosis repair (two), pulmonary lobectomy (one), and pleurectomy (one).

The blood loss was similar in the two groups and did not exceed 2000 ml. Patients with cirrhosis and control patients lost consciousness in 3.6 and 3.2 min, respectively (table II); loss of consciousness was smooth in all cases. Durations of infusions were similar for both groups. The infusion to cirrhotic patient No. 8 was discontinued before the end of the procedure because of transient haemodynamic instability. Patients with cirrhosis opened the eyes in 43 (33) min and control patients in 18 (5) min ($P < 0.05$). The mean blood concentration of propofol when the subject opened the eyes on verbal command was the same in both groups (1 µg ml^{-1}) (range 0.55–1.75 µg ml^{-1} for cirrhotic patients; 0.65–1.36 µg ml^{-1} for control patients).

Changes in mean blood concentrations of propofol with time, both during and after the infusion, followed a similar pattern in both groups of patients (figs 1, 2). Individual blood concentration of propofol data were fitted best by a triexponential function in seven and eight patients in the cirrhotic and control groups, respectively. Individual and mean values for pharmacokinetic parameters are recorded in table III for the model dependent and model independent analyses; the results for clearance were similar for both techniques. Clearance, and consequently C^{ss}, were not significantly different between cirrhotic and control patients and, similarly, there was no significant difference in values of V and the three half-lives. However, values of V^{ss} were significantly greater in patients with cirrhosis compared with control patients.

DISCUSSION

In all patients with cirrhosis, the severity of the liver dysfunction was moderate, allowing elective surgery. Five of the cirrhotic subjects had concentrations of albumin outside the normal range (< 30 g litre^{-1}).

Patients in both groups opened the eyes when blood concentration of propofol was about

TABLE II. *Weight and infusion details in cirrhotic and control subjects*

Patients	Weight (kg)	Loss of consciousness (min)	Duration of infusion (min)	Time to opening eyes (min)	Propofol infused (mg)	Concentration when opening eyes ($\mu g\ ml^{-1}$)
Cirrhotic						
1	69	2	141	104	1128	0.70
2	64	4	130	13	976	0.59
3	65	2	130	19	991	1.75
4	69	4	159	13	1252	0.55
5	51	3	120	14	727	0.70
6	80	3	218	57	1924	0.85
7	54	2.5	205	33	1229	1.50
8	60	5	61	—	501	—
9	75	4	160	70	1369	1.08
10	60	6	150	66	1059	1.08
Mean	64.7	3.6	147	43	1116	0.98
SD	9.0	1.3	44	33	382	0.42
Control						
1	60	3	142	24	987	0.91
2	55	4	226	16	1367	1.11
3	54	3	170	13	1040	0.70
4	55	2	296	18	1751	0.90
5	70	4	287	23	2167	1.13
6	85	4	180	25	1662	1.36
7	70	3	151	11	1101	1.23
8	61	3	133	10	949	0.79
9	96	3	162	20	1771	1.98
10	50	3	208	22	1153	0.65
Mean	65.6	3.2	196	18	1395	1.07
SD	14.9	0.6	58	5	418	0.40
P	ns	ns	ns	< 0.05	ns	ns

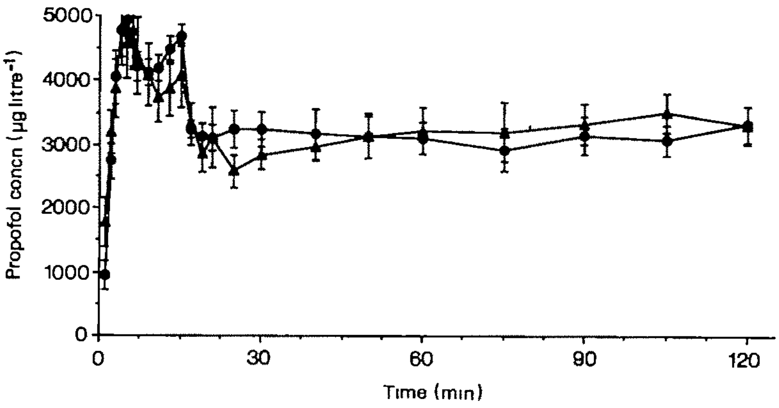

FIG. 1. Mean (SEM) blood concentrations of propopol with time during infusion of propofol in cirrhotic (●) and control (▲) groups.

1 $\mu g\ ml^{-1}$; this is in agreement with previously published data [10] and suggests that the pharmacological effects of propofol are not enhanced by cirrhosis. Four of the five subjects in the cirrhotic group with a delayed recovery (33–70 min) underwent a procedure to perform a portocaval shunt. It is known that the clearance of propofol is metabolic [2] and the high total body clearance from this and previous studies with both bolus [3, 11, 12] and infusion [1] administration

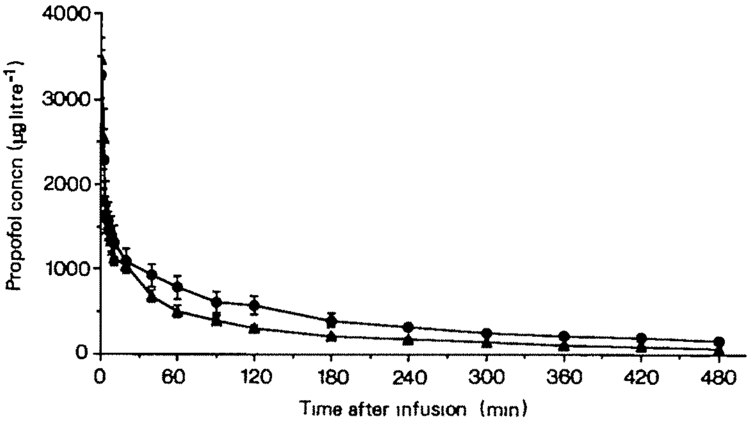

FIG. 2. Mean (SEM) blood concentrations of propopol with time after the infusion of propofol in cirrhotic (●) and control (▲) groups.

suggest that clearance is limited by total blood supply to the liver. However, extrahepatic mechanisms for clearance cannot be excluded [1, 13]. Procedures resulting in a reduction of total hepatic blood supply are likely, therefore, to result in reduced clearance of propofol. Porto-systemic anastomosis leads to reduced hepatic perfusion and the effect is greater with

TABLE III. *Pharmacokinetic parameters and compartmental analysis. mi = Model independent analysis; md = model dependent analysis; MRT = minimum residence time*

Patients	$T_{\frac{1}{2}}^{\lambda_1}$ (min)	$T_{\frac{1}{2}}^{\lambda_2}$ (min)	$T_{\frac{1}{2}}^{\lambda_3}$ (min)	*Cl* (mi) (litre min⁻¹)	V^{ss} (litre)	C^{ss} (µg ml⁻¹)	*V* (litre)	*Cl* (md) (litre min⁻¹)	MET (m[illegible])
Cirrhotic									
1	1.2	23	161	1.32	116	5.08	7.90	1.36	1[illegible]
2	2.1	23	381	1.88	330	3.21	11.40	1.99	24[illegible]
3	4.2	—	143	1.55	190	4.25	24.80	1.53	1[illegible]
4	1.0	26	318	2.36	263	2.83	5.73	2.44	1[illegible]
5	1.6	19	267	1.47	117	3.42	6.41	1.49	1[illegible]
6	4.7	—	191	2.30	272	3.80	25.10	2.11	2[illegible]
7	3.7	—	136	0.87	69	5.59	9.03	0.97	1[illegible]
8	2.3	35	254	1.28	206	4.37	10.80	1.37	19[illegible]
9	1.1	9	201	1.39	203	5.26	8.90	1.43	22[illegible]
10	2.0	20	288	1.18	251	5.02	16.60	1.20	29[illegible]
Mean	2.4	22		1.56	202	4.28	12.67	1.59	20[illegible]
SD	1.3	8		0.48	82	0.95	7.15	0.45	4[illegible]
Control									
1	—	22	245	1.61	144	3.37	—	1.78	16[illegible]
2	2.9	15	299	1.75	168	2.77	28.00	1.99	20[illegible]
3	1.9	—	129	1.29	38	3.93	5.72	1.37	11[illegible]
4	1.1	24	260	1.29	93	3.85	4.27	1.43	22[illegible]
5	2.1	—	115	1.97	132	3.41	12.80	2.05	21
6	2.8	30	213	1.93	101	3.92	19.00	2.17	14[illegible]
7	3.1	24	178	1.50	84	4.13	14.10	1.69	13[illegible]
8	1.6	19	190	1.92	90	2.89	8.25	2.11	11[illegible]
9	1.9	17	156	2.20	156	4.39	17.30	2.19	15[illegible]
10	2.5	39	336	2.02	203	2.49	13.70	2.01	20
Mean	2.2	24		1.75	121	3.52	13.68	1.88	16[illegible]
SD	0.7	8		0.32	49	0.63	7.32	0.30	4[illegible]
P	ns	ns		ns	< 0.05	ns	ns	ns	ns

portocaval compared with splenorenal shunting [14]. Thus, in the postoperative assessment period, patients who underwent portocaval shunting (patients Nos 7–10 in the cirrhotic group) would be expected to display reduced clearance of propofol. Clearance estimates from the fitted model for these subjects were low (0.87–1.39 litre min^{-1}). In the estimates of clearance derived from AUC_∞ for these subjects, the mean contribution to AUC_∞ from postoperative data was 41 (10) %. However, it is also possible that, in some or all of these patients, portocaval shunting was necessary to relieve portal hypertension resulting from a very high intrahepatic resistance to flow and consequent bleeding oesophageal varices. Preoperative hepatic perfusion might, therefore, have been low in these subjects. Despite the relatively low propofol clearance values in these subjects, mean clearance from the fitted model for the cirrhotic group was only about 10 % less than that in the controls; this difference was not statistically significant. These results confirm that, even at the propofol concentration required for maintenance of anaesthesia, hepatic blood supply rather than hepatic capacity is likely to be the limiting factor in the clearance of propofol by patients with moderate cirrhosis.

V^{ss} values for propofol in cirrhotic subjects administered a single bolus dose were similar to those in control subjects [3]; however, albumin concentrations in these cirrhotic subjects were greater than those in the present study. Propofol is highly bound to plasma proteins [3] and, being weakly acidic, is most likely to be bound to albumin. The blood concentrations of propofol observed in this study were within the range (up to 20 μg ml^{-1}) over which the proportion of bound drug was observed to remain constant in blood from subjects with normal albumin concentrations [I. D. Cockshott, unpublished data]. However, it is possible that endogenous compounds present in the blood of patients with cirrhosis could be competing with propofol for protein binding sites. In this circumstance, the greater free fraction would result in a larger volume of distribution. Despite the larger V^{ss} in the cirrhotic subjects, there was no apparent increase in the terminal elimination half-life.

Control patient values for V^{ss} are generally less than those estimated in our bolus dose study [3]. Estimates for this parameter and the terminal elimination half-life are sensitive to the duration of sampling [12]; for practical reasons the post-infusion sampling time in the present study had to be limited to 8 h, compared with 12 h in the bolus dose study. The mean V^{ss} value reported by Gepts and colleagues [1] for a 2-h infusion of 6 mg kg^{-1} h^{-1} and sampling for 8 h after infusion was also greater (332 litre) than that in the present study, but intersubject variability in Gepts' study was large (SD 257 litre).

It is concluded that the pharmacokinetics of propofol given by infusion are not affected markedly by moderate cirrhosis. Thus propofol appears to be suitable for maintaining general anaesthesia in cirrhotic patients suitable for elective surgery. As already reported [10], considerable interindividual variability exists in normal subjects and careful titration of the infusion rate based on clinical response is necessary in all patients.

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EFFECT OF PROPOFOL ON PERIPHERAL VASCULAR RESISTANCE DURING CARDIOPULMONARY BYPASS

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J. VAN DER KROGT

SUMMARY

Twenty-eight patients undergoing elective coronary artery bypass surgery were allocated randomly to receive either propofol 2 mg kg^{-1} or an equivalent volume of its vehicle during cardiopulmonary bypass with constant pump flow. Peripheral vascular resistance (PVR) was calculated from perfusion pressure and pump flow. After propofol, PVR decreased from 1767 (SD 415) dyn s cm^{-5} to a minimum of 1263 (283) dyn s cm^{-5} at 2 min, and remained significantly less than the control value until 12.5 min after administration of propofol. In the group given the vehicle, PVR did not change significantly. In a second study in 10 patients, venous blood samples were withdrawn before and 2, 4, 6, 8, 10, 20 and 30 min after injection of propofol 2 mg kg^{-1} during cardiopulmonary bypass, for measurement of blood concentrations of propofol. Concentrations were greater than predicted by a computer simulation based on published pharmacokinetic data. The decrease in PVR may be an important factor in the hypotension caused by propofol during induction of anaesthesia.

KEY WORDS

Anaesthetics intravenous propofol, blood concentration. Surgery: coronary artery.

Propofol, given as an i.v. bolus for induction of anaesthesia, commonly causes hypotension which is dose related, and is less when the drug is administered slowly [1]. Propofol appears to cause more hypotension than equivalent doses of thiopentone [1–3]. This may be related to the greater decrease in peripheral vascular resistance (PVR) caused by propofol [4]. The decrease in PVR is comparable to the decrease in arterial pressure, suggesting that vasodilatation may be a major factor in propofol-induced hypotension.

Other contributing factors may be a lesser increase in heart rate in response to hypotension and impairment of myocardial contractility. Propofol causes resetting of the baroceptor reflex control of heart rate without depression of baroreflex sensitivity [5]. This allows low heart rates to be sustained despite a decrease in arterial pressure. Both in patients without cardiac disease and in those with severe coronary artery disease, propofol causes about a 20% decrease in cardiac index [6–8] which is similar to that caused by thiopentone [7]. There is evidence that propofol does not alter left ventricular performance in patients with coronary artery disease and good left ventricular function [8]. However, other studies in cardiac surgical patients suggest that the drug may cause some myocardial depression in addition to vasodilatation [7, 9]. This may be secondary to a reduction in coronary artery blood flow consequent upon hypotension [10].

Cardiopulmonary bypass has been used as a model to study the isolated effects of drugs on the peripheral circulation [11–14]. We have used this model to investigate the effect of propofol on PVR in two consecutive studies. The first study was a double-blind comparison of the effects of propofol and its vehicle on PVR. In the second study, the changes in blood concentrations of propofol were measured also.

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PATIENTS AND METHODS

After informed consent had been obtained, we studied patients undergoing elective aorto-coronary bypass grafting surgery. Both studies were approved by the local Ethics Committee.

Study one

Twenty-eight patients were premedicated with lorazepam 2–4 mg sublingually, 90 min before arriving in the operating theatre. Anaesthesia was induced with sufentanil 4–8 μg kg^{-1}. Pancuronium 100 μg kg^{-1} was given for muscle relaxation and, after intubation of the trachea, the lungs were ventilated with an oxygen–air mixture ($F\text{I}_{\text{O}_2} = 0.5$). Anaesthesia was maintained with sufentanil 0.05–0.1 μg kg^{-1} min^{-1}, but during cardiopulmonary bypass the infusion of sufentanil was reduced to 0.025 μg kg^{-1} min^{-1}. Cardiopulmonary bypass was conducted with a membrane oxygenator using non-pulsatile flow and moderate hypothermia (26–27 °C). The circuit prime consisted of Ringer's solution 1400 ml, human albumin 200 ml and 20% mannitol 100 ml. In all patients, systemic arterial pressure measured in a radial artery was taken to indicate perfusion pressure during cardiopulmonary bypass.

Any patient who had been given a vasoactive drug before or during cardiopulmonary bypass was excluded from the study. When nasopharyngeal temperature and pump flow had been stable for 5 min during cardiopulmonary bypass, with a perfusion pressure greater than 50 mm Hg, a bolus of 0.2 ml kg^{-1} of a coded solution containing either propofol 10 mg ml^{-1} or Intralipid was injected over 30 s into the venous inflow line of the oxygenator. Perfusion pressure, pump flow and temperature were recorded at 30-s intervals for a minimum of 10 min. Measurements were continued until cardioplegic solution was given, the pump flow was changed, or the aortic clamp was released.

Venous blood samples were withdrawn for measurement of plasma concentrations of adrenaline and noradrenaline immediately before administration of the study drug and either at the time of maximum decrease of perfusion pressure or 5 min after administration of drug. A 3-ml blood sample was placed in a cooled tube containing 60 μl of a solution of reduced glutathione 60 mg ml^{-1} and EDTA 50 mg ml^{-1}. The samples were stored in melting ice and the plasma separated within 15 min in a refrigerated centrifuge (4 °C). Plasma was stored at −20 °C until assayed. Catecholamines were assayed radioenzymatically [15].

Study two

This study involved 10 patients. The technique of anaesthesia and cardiopulmonary bypass and the pre-study conditions were the same as those for study one. When stable conditions had been present during cardiopulmonary bypass for 5 min, propofol 2 mg kg^{-1} was injected over 30 s into the venous inflow line of the oxygenator. Perfusion pressure, pump flow and temperature were measured as described above.

Venous blood samples were withdrawn from the internal jugular vein before and 2, 4, 6, 8, 10, 20 and 30 min after injection of propofol for measurement of blood concentrations. Samples were stored at 4 °C until assayed. Propofol concentrations were measured in blood by a modification of the method described by Adam and colleagues [16, 17].

PVR was calculated as:

$$\frac{\text{perfusion pressure (mm Hg)}}{\text{pump flow (litre min}^{-1}\text{)}} \times 80 \text{ dyn s cm}^{-5}$$

Data were analysed by two-way analysis of variance for repeated measures. When indicated, differences within or between groups were tested using paired and unpaired t tests with Bonferroni correction for multiple comparisons. $P < 0.05$ was accepted as statistically significant. Results are presented as mean (SD).

RESULTS

There were no significant differences in patient data, pre-drug pump flow, perfusion pressure, Pa_{O_2} or packed cell volume between the two groups of patients in study one, or between patients in the two studies (table I).

Study one

Data were collected from all patients for 8 min after administration of propofol, and in 10 patients for 12.5 min. In the Intralipid group, data were collected from all patients for 6 min and from 10 patients for 8.5 min. Following administration of propofol, PVR decreased, reaching a minimum value of 1263 (283) dyn s cm^{-5} at 2 min. This was

TABLE I. *Demographic data and pre-drug conditions in studies one and two (mean (SD))*

	Study one		Study two
	Propofol	Intralipid	Propofol
Number of patients	14	14	10
Age (yr)	60.4 (6.6)	64.4 (9.3)	58.0 (7.0)
Weight (kg)	81.8 (13.0)	76.1 (8.2)	79.6 (11.6)
BSA (m^2)	1.94 (0.175)	1.89 (0.15)	1.92 (0.19)
Perfusion pressure (mm Hg)	65.8 (10.9)	68.9 (8.9)	60.7 (6.6)
Flow (litre min^{-1})	3.16 (0.29)	3.16 (0.13)	3.12 (0.31)
Pa_{O_2} (kPa)	22.3 (9.7)	19.7 (6.9)	21.1 (4.8)
PCV	0.26 (0.03)	0.26 (0.03)	0.26 (0.04)

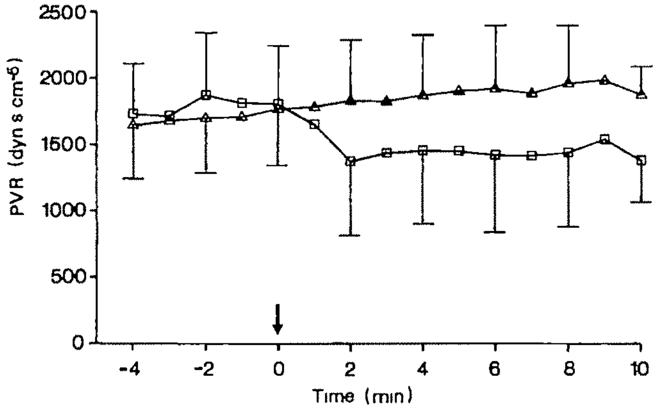

FIG. 1. Peripheral vascular resistance (PVR) after propofol 2 mg kg^{-1} (□) or an equivalent volume of its vehicle (△) during cardiopulmonary bypass for aortocoronary bypass surgery.

significantly ($P < 0.001$) less than the average of values obtained in the 4 min before administration of drug (control value: 1767 (415) dyn s cm^{-5}). PVR remained significantly less than the control value until 12.5 min after administration of propofol, but did not change significantly during the 10-min observation period following administration of Intralipid (fig. 1). There were no changes in plasma concentration of adrenaline or noradrenaline in each group (table II).

TABLE II. *Plasma concentrations of adrenaline and noradrenaline (mean (SD)) before and after administration of propofol 2 mg kg^{-1} or an equivalent volume of its vehicle (Intralipid). Blood samples for the measurement of post-drug concentrations were taken either at time of maximum decrease in perfusion pressure or at 5 min after administration of drug*

	Propofol	Intralipid
Adrenaline (pmol ml^{-1})		
Before	2.4 (2.2)	1.7 (1.5)
After	1.8 (1.5)	1.6 (1.4)
Noradrenaline (pmol ml^{-1})		
Before	3.0 (2.0)	4.1 (2.5)
After	2.5 (1.3)	3.6 (2.3)

TABLE III. *Mean (SD) changes in peripheral vascular resistance (PVR) following propofol 2 mg kg^{-1} in the two studies*

Time relative to administration (min)	Change in PVR (dyn s cm^{-5})	
	Study one	Study two
Control	1767 (415)	1590 (214)
2	1263 (283)	1322 (341)
4	1328 (320)	1315 (258)
6	1302 (330)	1312 (269)
8	1310 (312)	1372 (267)
10	1373 (235)	1404 (269)

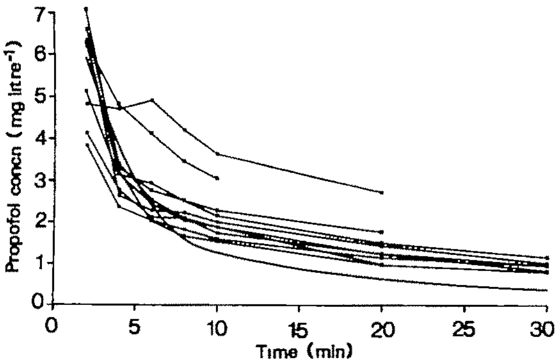

FIG. 2. Whole blood concentrations of propofol in 10 patients at timed intervals after administration of propofol 2 mg kg^{-1} during cardiopulmonary bypass for aortocoronary bypass surgery (——). The thicker, continuous line (——) is the change in propofol concentration following the same dose predicted by a computer simulation based on pharmacokinetic data [18].

Study two

The changes in PVR following administration of propofol were similar to those in study one (table III).

The changes in blood concentrations of propofol for individual patients are shown in figure 2. Initially, they decreased rapidly, presumably as a result of distribution, and then from about 6 min decreased more slowly. In all patients, blood concentrations of propofol from 8 min after administration were greater than that predicted by the pharmacokinetic model described by Gepts and colleagues [18].

DISCUSSION

Haemodynamic changes after induction of anaesthesia are the result of both direct and indirect effects on the myocardium and peripheral blood vessels. The indirect effects are mediated by changes in peripheral receptors and central control mechanisms. Under normal circumstances, it may be difficult to isolate the contribution that individual mechanisms make to the overall haemodynamic response to a drug. Cardiopulmonary bypass has been shown to be a useful model for studying the isolated effects of anaesthetic drugs on PVR; it has been used to study the effect of morphine [11], benzodiazepines [12], droperidol [13] and thiopentone [14]. Using this model, we have found that propofol 2 mg kg^{-1}, given during cardiopulmonary bypass under stable conditions of perfusion pressure, flow and temperature, caused a rapid decrease of 28% in perfusion pressure and thus of PVR. This decrease is comparable to that observed in studies when propofol was given for induction of anaesthesia. Propofol 2 mg kg^{-1} given to patients undergoing elective general surgery caused a 18–22% decrease in PVR [19]. When propofol 1.5 mg kg^{-1} was used to induce anaesthesia in patients undergoing elective coronary artery bypass surgery, PVR decreased by 19% [20].

Studies of the effects of drugs on peripheral vascular tone commonly rely on estimates of vascular resistance, based on the ratio of pressure and flow (cardiac output), before and after drug administration. Valid conclusions based on these estimates depend on the assumption of a linear pressure–flow relationship that passes through the origin. This is often not the case [21], so that isolated resistance calculations cannot discriminate between changes in pressure caused by active changes in vascular tone and passive changes resulting from altered venous return [22]. However, this does not apply to our model in which flow is independent of venous return. Furthermore, all our studies were performed during constant flow rate conditions.

In our first study, the decrease in PVR caused by propofol lasted for more than 10 min. This is in contrast to other studies, in which the reduction in PVR was of short duration. However, in those studies patients underwent laryngoscopy and intubation of the trachea within a few minutes after administration of propofol. It is possible that, had this not occurred, the decrease in PVR would have been more prolonged. A possible explanation of the prolonged reduction of PVR in our patients could be altered propofol pharmacokinetics during cardiopulmonary bypass, resulting in greater concentrations in blood than would occur after the same dose given for induction of anaesthesia. In order to investigate this, we studied the changes in concentration of propofol following a bolus injection of propofol 2 mg kg^{-1} in a second group of patients. Although our results did not allow detailed pharmacokinetic analysis, they suggest that blood concentrations of propofol decreased more slowly during bypass than in patients given a similar dose of propofol for induction of anaesthesia.

It is reasonable to assume that the direct effects of propofol on vascular smooth muscle are proportional to its concentration in blood. The greater blood concentration of propofol in our patients compared with those predicted in patients not subjected to cardiopulmonary bypass, may partly explain the prolonged reduction in PVR. Cardiopulmonary bypass is known to alter significantly the disposition of many drugs as a result of haemodilution, hypotension, hypothermia and altered regional blood flow [23]. It is also possible that hypothermia (26–27 °C) may have altered the sensitivity of vascular smooth muscle to the effects of propofol. The use of non-pulsatile flow also may have contributed to the duration of the resistance decrease. Videcoq and colleagues [13] found that the decrease in vascular resistance produced by droperidol was of shorter duration with pulsatile flow.

Propofol is a weak organic acid that is bound extensively to plasma albumin, with a free fraction of only 2–3% [24]. Haemodilution during cardiopulmonary bypass is associated with proportional decreases in the concentrations of plasma proteins, and a 1.5–3 fold increase in the fraction of unbound propofol [25]. An increased free fraction of propofol could have contributed to the prolonged effect observed in our patients. The use of heparin during cardiopulmonary bypass causes an increase in non-esterified fatty acids because of activation of lipoprotein lipase [26]. Non-esterified fatty acids are thought to be responsible for the decrease in drug binding to plasma proteins after heparin [27]. This could be an additional explanation for our findings.

Unfortunately, because of the type of bypass circuit used in our study, we were not able to evaluate the effect of propofol on capacitance vessels. However, the finding that perfusion pressure and thus PVR decreased significantly after administration of propofol, with perfusion flow maintained constant, implies that propofol caused arteriolar vasodilatation. This could have been secondary to a reduction in sympathetic outflow caused by deepening of anaesthesia. However, the fact that catecholamine concentration did not change suggests that the haemodynamic effect of propofol was the result of direct action on blood vessels.

Although our results confirm the importance of changes in PVR to the overall haemodynamic response to propofol, they cannot be extrapolated directly to other clinical situations. Our results have been influenced by the special factors present during cardiopulmonary bypass, in particular haemodilution, hypothermia and the use of non-pulsatile blood flow. These factors should be taken into consideration when interpreting the findings of this study.

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EFFECT OF FLUMAZENIL ON MIDAZOLAM-INDUCED AMNESIA

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SUMMARY

We have studied the effect of i.v. flumazenil 0.01 mg kg^{-1} on the amnesia and sedation caused by midazolam 2 mg and 5 mg i.v. in volunteers in order to determine the relationship between the actions of the antagonist on these two effects. Midazolam caused dose-dependent central neural depression as assessed by critical flicker fusion frequency, and dose-dependent amnesia for word cards. In subjects given flumazenil 5 min after administration of midazolam, fusion frequency readings and memory were restored to levels comparable to those before midazolam administration. These two effects of flumazenil were similar in time course and extent, suggesting that they share the same mechanism of action. Flumazenil given alone had no effect on memory. The study has demonstrated anterograde amnesia following benzodiazepine administration and antagonism by flumazenil. There was neither retrograde amnesia nor retrograde antagonism of amnesia.

KEY WORDS

Antagonists benzodiazepine: flumazenil. Hypnotics benzodiazepine: midazolam. Memory: amnesia.

The specific benzodiazepine antagonist flumazenil has little agonist activity, but binds competitively to the benzodiazepine receptor, blocking the actions both of benzodiazepines and of inverse agonists such as beta-carbolines [1]. The major limitation to its routine use would appear to be its short elimination half-life [2] (49–58 min), which is shorter than that of clinically used benzodiazepines, so that resedation is at least a theoretical possibility.

It has long been recognized that benzodiazepine-induced sedation is accompanied by anterograde amnesia, in that patients may appear to be fully aware of events and conversations, but are found subsequently to have no memory. With the exception of lorazepam, the amnesia is reliable only when the drugs are given i.v. [3]. The duration of amnesia is dose-dependent [4].

In recent years, midazolam has become the drug of choice in most situations in acute care in which the use of a parenterally administered benzodiazepine is indicated. This water soluble imidazo-benzodiazepine is associated with a low incidence of pain on i.v. injection and of venous sequelae [5] and has a comparatively short elimination half-life, with no significant pharmacologically active metabolites [6]. In 1980, Dundee and Wilson [7] showed that, when given i.v. in a dose of 5 mg, midazolam caused dense anterograde amnesia of 5–15 min duration, followed by a variable period of less profound amnesia.

Clearly, it is important to be able to predict the nature, extent and duration of the effect of flumazenil on the amnesia produced by i.v. midazolam, particularly in comparison with its effect on the level of sedation. We have therefore adapted the method of Dundee and Wilson to study, first, the effects of two commonly used clinical doses of midazolam, administered i.v., on memory of precisely timed stimuli presented over a period of a few minutes after injection, while at the same time assessing the degree of central neural depression; second, the effects on these observations of subsequent i.v. administration of flumazenil in the recommended dose range; and third, the effects of this dose of flumazenil when not preceded by midazolam.

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SUBJECTS AND METHODS

We studied six healthy volunteers (mean age 34 yr, mean weight 68 kg) on six morning sessions, separated by at least 1 week, so that each received once, in random order, all of the following drug combinations: midazolam 2 mg–saline (M2S); midazolam 5 mg–saline (M5S); midazolam 2 mg–flumazenil (M2F); midazolam 5 mg–flumazenil (M5F); saline–flumazenil (SF); saline–saline (SS). Subjects were unaware of the sequence.

The Leeds Critical Flicker Fusion Frequency Monitor [8] was used to assess the subjects' degree of central neural depression. This instrument has four light-emitting diodes which are placed 60 cm horizontally in front of the subject and, when activated by the observer, flicker with a frequency which increases or decreases at a rate of 1 Hz s^{-1} between 10 Hz and 50 Hz. The subject presses a button when the flicker appears subjectively to fuse into a steady light if frequency is increasing, or to become apparent if frequency is decreasing. The machine records this as the critical flicker fusion frequency (CFFF). Because the study was designed to measure rapidly occurring changes in the level of central neural arousal, one ascending and one descending frequency reading only were obtained at each CFFF measurement point and the mean of these calculated.

A sequential plan of the study is shown in figure 1. After four trial runs made over a period of 10 min, subjects recorded an initial CFFF score immediately before time 0, the start of the session. The first of the two drug treatments, midazolam 2 mg, midazolam 5 mg or saline in 2.5 ml was given over 20 s, beginning 1 min after the start of the session. The second treatment, either 0.01 mg kg^{-1} flumazenil or saline in 5.5–8.0 ml, was given over 40 s after a further 5 min.

At time 0 and after 0.5, 2.0, 2.5, 4.0, 4.5, 7.0, 7.5, 9.0, 9.5, 11.0 and 13.0 min, subjects were shown postcards, one at each time, on each of which one word was written in large letters. Thus two cards were shown before the first drug treatment, four between treatments and the remaining six after the second treatment. The cards were displayed for 3 s and the subjects read the words aloud. No other conversation took place. The words were concrete nouns chosen to occur at a frequency of between 1 in 10^5 and 1 in 10^6 in general use [9]. Sets of word cards were rotated so that the same combination of set of words and treatment group was not used more than once, but the 12 words within each set were used always in the same order.

After 3, 5, 8 and 10 min from time 0—that is, twice between drug treatments and twice after the second treatment—further CFFF scores were obtained.

The sequence of injections, word card display and CFFF recordings lasted 13 min, after which subjects rested quietly until 2 h after time 0. A final CFFF score was obtained.

Subjects were subsequently shown, one by one and in random order, a set of 24 word cards containing the 12 previously shown, mixed with 12 others. They were asked to identify those already seen. Memory of cards was scored as one point for complete recognition of a card and half a point for uncertain or hazy recognition, giving a maximum possible score of six points per treatment group per word card. New sets of dummy cards were used for each subject on each occasion.

The CFFF data were analysed as a whole using the Kruskal–Wallis test. Where significant differences were shown, further analysis of individual inter-group differences was carried out using the Mann–Whitney *U* test. The memory data were analysed using Fisher's exact test of

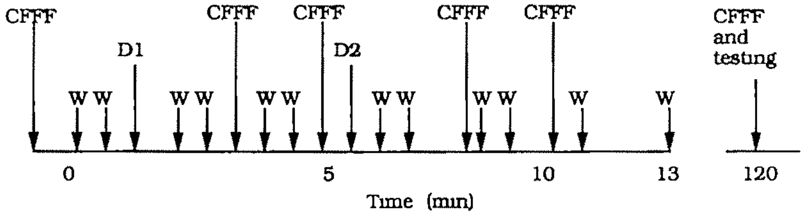

FIG. 1. Sequential plan of the study. W = Presentation of word card; CFFF = critical flicker fusion frequency; D1 = first treatment (midazolam 5 mg or 2 mg or saline); D2 = second treatment (flumazenil 0.01 mg kg^{-1} or saline).

probability. Analysis was two-tailed, and a significance level of $P < 0.05$ was used for all tests.

RESULTS

Critical flicker fusion frequencies

There were no significant differences among the six treatment groups in mean CFFF scores taken before commencement of the sessions. At 3 min (2 min after the administration of midazolam 2 mg or 5 mg or saline), CFFF scores in the two groups given midazolam 5 mg (M5 groups) had decreased ($P < 0.01$) below those in the two saline (S) groups. However, although there was a reduction in CFFF scores in the two groups given midazolam 2 mg (M2 groups), these scores did not differ significantly from either the S or the M5 groups. The same pattern was seen at the 5-min reading (table I).

At 8 min (2 min after administration of either flumazenil 0.01 mg kg^{-1} or saline), mean CFFF score had recovered in the M5F group to the extent that it was no longer different from that in the S groups, while in the M5S group, which did not receive flumazenil, the score was significantly less than that in both the S groups and the M5F group. Again, similar but non-significant changes were seen in the M2 groups. A similar pattern of changes was seen in all groups at 10 min.

By 2 h after the beginning of the session, there were no significant differences in CFFF scores among the six treatment groups.

With regard to changes within the treatment groups during the period of the study, there were no significant changes in CFFF scores in either of the two S groups. In the M5S group, the four scores after midazolam administration were significantly less than the initial values, while in the M5F group, scores were reduced significantly at 3 and 5 min, but after flumazenil administration were again comparable to initial values. Again, changes in the M2 groups were similar but less marked. By the final reading at 2 h, mean CFFF scores in all groups were not significantly different from initial values.

Memory

The summed amnesia scores of the six subjects for each of the 12 word cards in all six treatment groups are shown graphically in figure 2. In the two S groups, most subjects recognized most of the words when they were shown again 2 h later, with no significant differences between these two groups. In all four midazolam groups, recognition of the two cards shown before any drug was given was almost complete. However, for word cards shown after midazolam administration but before the second drug treatment, memory was reduced markedly in the two M2 groups and virtually abolished in the two M5 groups. In all four midazolam groups, these scores were significantly different ($P < 0.01$) both from the S groups and from the pre-midazolam scores. In the M2S and M5S groups, memory did not improve for the remaining six cards. In the two groups given midazolam followed by flumazenil, memory of word cards shown after administration of flumazenil was markedly improved, so that scores in these groups were now comparable to those in the S groups and to the pre-midazolam scores, but significantly different from both the pre-flumazenil scores and the post-saline scores in the MS groups.

TABLE I. *Mean (SEM) critical flicker fusion frequency scores in the six treatment groups at the times shown. SS = Saline–saline; SF = saline–flumazenil; M5S = midazolam 5 mg–saline; M5F = midazolam 5 mg–flumazenil; M2S = midazolam 2 mg–saline; M2F = midazolam 2 mg–flumazenil. Drug 1 = midazolam 2 mg or 5 mg or saline; Drug 2 = flumazenil* 0.01 *mg kg*$^{-1}$ *or saline*

Time (min)	SS	SF	M5S	M5F	M2S	M2F
Baseline	35.63 (1.086)	33.71 (1.191)	33.78 (0.795)	34.60 (0.673)	34.24 (0.846)	34.92 (0.879)
Drug 1						
3	34.71 (1.024)	33.94 (0.956)	25.32 (1.736)	25.38 (1.963)	29.63 (0.937)	30.51 (1.505)
5	34.68 (1.322)	33.69 (1.117)	27.19 (2.412)	27.03 (1.805)	29.98 (1.684)	31.47 (0.943)
Drug 2						
8	34.15 (1.109)	32.75 (0.950)	26.59 (2.130)	32.04 (0.686)	30.18 (1.969)	32.96 (1 177)
10	33.80 (0.672)	32.89 (0.858)	27.05 (2.239)	32.34 (0.977)	30.42 (2.257)	32.42 (1.013)
120	32.98 (1.277)	32.97 (1.193)	30.89 (0.758)	32.53 (1.107)	32.75 (0.892)	34.60 (1.488)

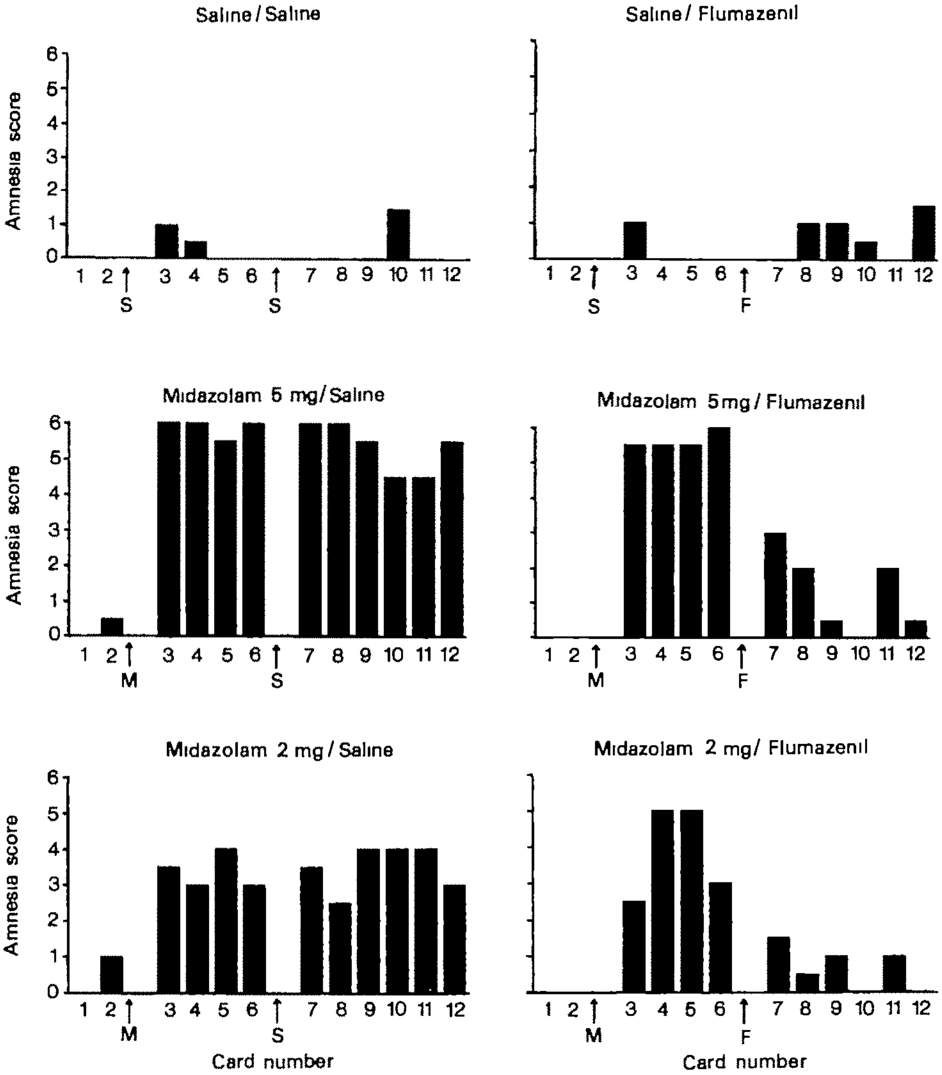

FIG. 2. Total amnesia scores of the six subjects for each of the 12 word cards in all six treatment groups. The times of administration of saline (S), midazolam (M) 2 mg or 5 mg or flumazenil (F) 0.01 mg kg^{-1} are indicated by the arrows.

DISCUSSION

This study has shown that the amnesic effects of two doses of midazolam administered i.v. were antagonized by subsequent administration of i.v. flumazenil 0.01 mg kg^{-1}. The time course and relative extent of the anti-amnesic action of flumazenil were similar to those of its anti-sedative action. A further finding was that flumazenil alone had no effect either on the level of central neural arousal or on memory.

Benzodiazepine-induced amnesia has been studied extensively, often in situations relevant to the use of the drugs in clinical anaesthesia, and some of its characteristics are well established [10]. In most studies, the model of memory function used has been that of Atkinson and Shiffrin [11], which assumes that memory consists of three components: a very transient sensory memory, a limited capacity short term memory of some seconds duration and a long term memory store with an effectively unlimited capacity. It has been found consistently that only the last of these is impaired reliably by benzodiazepines [12]. Further, it is established that material already in the memory store is not affected—that is, there is no retrograde amnesia, the presence of which might have suggested that a process such as retrieval of information or the speed of decay of the memory trace was being affected. These observations have led most authors to conclude that the drugs act on the "consolidation" process, whereby recently acquired material is transferred from short term memory to the long term memory store.

In this study, midazolam produced closely related, dose-dependent amnesia and sedation. Similar observations have led some workers to argue that the amnesic effect is not specific but part of the global sedative effect of benzodiazepines [13, 14], perhaps through prevention of rehearsal of new material. However, in several studies, mainly in the clinical anaesthesia field, benzodiazepines have been compared with opioids [12, 15], butyrophenones [16], phenothiazines [17, 18] and barbiturates [19, 20], and have been found in each case to have a greater amnesic effect at approximately equi-sedative doses. Thus the sedation produced by benzodiazepines is different from that of comparable doses of other groups of drugs in that it is accompanied by anterograde amnesia, a specific effect upon the learning process.

In the present study, the close relationship between benzodiazepine-induced sedation and amnesia is confirmed further in that both were antagonized similarly by flumazenil. In the M2F and M5F groups, both CFFF and amnesia scores had returned to pre-midazolam values by 3 min after administration of flumazenil. This suggests that these two actions are mediated by the same receptor in the CNS, and that some of the GABA-ergic inhibitory pathways which are facilitated by benzodiazepines are involved in the control of the laying down of long term memory. These pathways are located in the cerebral cortex and hippocampus in addition to other regions [21], while the currently available evidence on the localization of memory in the mammalian brain suggests that, while the hippocampus is widely involved in learning, the site of long term storage is elsewhere—perhaps in the cortex [22].

This study provides further evidence that the established theory of the mechanism of benzodiazepine-induced amnesia is correct. As expected, there was no evidence of a retrograde amnesic action of midazolam, the two cards shown before its administration being recognized in almost every case. In addition, flumazenil prevented amnesia only of word cards shown after its own administration—there was no "retrograde reversal" of amnesia. It appears, therefore, that material presented before flumazenil was given was already lost by the time this occurred, 1.5 min after the sixth card was shown. At the time that the memory assessments were carried out, 2 h after the commencement of the study, CFFF scores were not significantly different from initial values, and there were no inter-group differences. Thus it is unlikely that the presence of a residual drug effect contributed to the memory scores obtained at this time. It seems, therefore, that the amnesic action of midazolam occurs through an effect on a process that normally begins within 1–2 min following the presentation of material.

Our findings confirm that flumazenil alone in this dose had no effect on central neural arousal as measured by the CFFF score, and also indicate that it had no effects on memory. However, three of the six subjects in the SF group reported slight anxiety or dysphoria lasting less than 30 s following injection of flumazenil, a finding which has been noted by others [23, 24].

Other workers have also reported antagonism of benzodiazepine-induced amnesia by flumazenil. However, in most cases this was noted only as part of a general assessment of the effects of the antagonist and the method of memory testing was either inadequately controlled [25], unspecified [26] or designed in such a way that amnesia and sedative effects could not be separated [27].

Ghoneim, Dembo and Block [28] compared the effects of flumazenil and placebo on immediate and delayed word list recall and recognition and on subjective ratings of mental and physical sedation in patients who had received diazepam sedation for dental surgery. Their results revealed a difference between the effects of flumazenil on subjectively-rated mental sedation, which was restored to pre-surgery scores, and the effects on physical sedation and memory, which were restored only partly, over a period of up to 2 h after administration of flumazenil. In our own study, no difference was found between sedation and amnesia, perhaps largely because of differences in the methods of assessment of memory and sedation. The method of memory assessment, card recognition, used in the present study is undoubtedly less taxing than the word list recall and recognition tasks used by Ghoneim and colleagues, and it is possible that a more difficult task might have revealed residual amnesia following flumazenil administration. However, this method has been found in the past to be a reliable method of assessing drug-induced amnesia in the clinical setting [3, 4, 15], especially when the aim is to study rapid changes over a short time as in this study. The critical flicker fusion frequency test has been shown to provide a sensitive assessment of central processing of perceptual information [29], and it proved well suited to the rapid, frequent measurements required in the present study. However, it clearly gives a view of cerebral function from a different angle than the subjective ratings used by Ghoneim's group.

From the clinical point of view, it would appear from these findings that, when flumazenil is used to antagonize midazolam-induced sedation, the ability to remember events occurring during the period of antagonism is also restored. This is an advantage when the antagonist is used following benzodiazepine sedation in dentistry or endoscopy. However, the clinical situation which is most closely mimicked by the design of this study is the use of flumazenil for temporary reversal of benzodiazepine-induced sedation for neurological assessment, and in this case it is unfortunate that, on this evidence and with these doses of midazolam and flumazenil, patients may probably remember these unpleasant experiences.

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MEASUREMENT OF ENTRAINMENT RATIO DURING HIGH FREQUENCY JET VENTILATION

M. J. JONES, S. D. MOTTRAM, E. S. LIN AND G. SMITH

SUMMARY

We have measured tidal (V_T), entrained (V_e) and "blowback" (V_{bb}) volumes during high frequency jet ventilation (HFJV) through a Mallinckrodt Hi-Lo Jet tracheal tube in anaesthetized patients. The above volumes were calculated by digital integration of the appropriate regions of flow curves derived from a pneumotachograph placed between the bias flow tubing and the tracheal tube. At a driving pressure of 1 bar, lung minute ventilation increased with increasing ventilatory frequency, whilst tidal volumes decreased. The contribution of entrainment to tidal volume (V_e/V_T) remained constant, although the volumes entrained were relatively small and varied widely from subject to subject. Blowback volumes were considerable, especially at ventilatory frequencies used clinically (1–2 Hz). We conclude that it is not possible to entrain predictable concentrations of volatile agents from the low pressure bias flow during HFJV.

KEY WORDS

Lung: high frequency jet ventilation.

The clinical use of high frequency jet ventilation (HFJV) in anaesthesia is limited by inability to introduce volatile agents into the high pressure system. However, it is known that a significant proportion of lung ventilation arises from entrainment of gas [1]. Ability to quantify the extent of entrainment raises the possibility of anaesthetizing patients predictably by introduction of volatile agents into the low pressure bias flow.

Lung ventilation during HFJV is a complex function and depends on the volume of gas delivered with each jet pulse (Vjet), the volume of gas entrained (Ve) and the volume of gas blown back (Vbb) into the bias flow. Previously, measurement of these gas volumes required complex techniques such as box plethysmography [2] or external spirometry [3], or failed to recognize the existence of blowback [4, 5] (i.e. the escape of a volume of jet gas from the tracheal tube into the bias flow during late inspiration, without entering the lungs). Although these volumes have been measured successfully *in vitro* using a lung model [6], there are currently no satisfactory published studies in human subjects.

In previous experimental studies from this department, simple differential pressure measurements from within the tracheal tube were used to produce gas flow curves [7]. This system has been modified by the measurement of flow between the bias flow tubing and the tracheal tube, using a pneumotachograph. This enabled the measurement of tidal, entrained and blowback volumes by partial integration of the flow curves. With this system, we have studied the variation of the contribution of entrainment to tidal volume (termed entrainment ratio) in patients with alteration of ventilatory frequency and inspiration:expiration time ratios.

PATIENTS AND METHODS

Patients

We studied 12 patients (age 40–97 yr, ASA II–III) undergoing surgery for fractured neck of femur. The study was approved by the District Ethics Commiteee and all patients gave informed consent. Anaesthesia was induced with fentanyl 0.1 mg and propofol 1.0 mg kg^{-1} and, following the administration of vecuronium 0.08 mg kg^{-1}, the trachea was intubated using a Mallinckrodt

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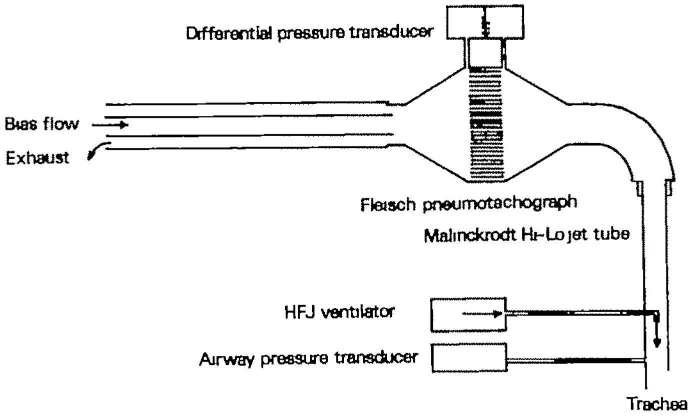
Differential pressure transducer
Bias flow
Exhaust
Fleisch pneumotachograph
Malinckrodt Hi-Lo jet tube
HFJ ventilator
Airway pressure transducer
Trachea

FIG. 1. Schematic diagram of the system used for measurement of gas volumes during jet ventilation.

Hi-Lo Jet tube. Anaesthesia was maintained with an i.v. infusion of propofol according to the dose regimen described by Roberts and colleagues [8]. All patients were monitored with continuous ECG and pulse oximetry recordings, and by non-invasive measurement of systemic arterial pressure.

Experimental apparatus (fig. 1)

HFJV was applied using a Penlon Bromsgrove jet ventilator [9] and a bias flow, both supplying an $F\mathrm{I}_{\mathrm{O}_2}$ of 1.0. The bias flow was delivered from a conventional Bain system, the distal end of which was attached to a Fleisch No. 3 pneumotachograph head (Gould, Bilthoven) connected to a capacitive differential pressure transducer. The linear range of the flow transducer was 0–160 litre min^{-1}, and the apparatus had a frequency response flat to 16 Hz (−3 dB at 32 Hz, 95% step response time 0.015 s). The pressure relief valve of the Bain system was opened fully and the bias flow adjusted so that the reservoir bag remained semi-inflated at all times. This ensured that the bias circuit remained at atmospheric pressure. Bias flows were typically 1 litre min^{-1}. Rebreathing was not found to be a problem, presumably because most of the respiratory gas was injected directly into the tracheal tube. The attachment of the pneumotachograph head to the tracheal tube was made via a conical rubber adaptor, in order to produce a smooth velocity profile at the pneumotachograph screen. Failure to do this might have resulted in a higher gas velocity (and hence pressure decrease) at the centre of the screen, which would not be detected by the peizometer rings, as these sense pressure changes across the screen at its periphery. Any tendency for this to occur was compensated for by carrying out the calibration procedure (see below) with the tracheal tube connected.

Data were collected from the flow transducer using a Gould 1604 digital storage oscilloscope. Gas volumes were obtained by partial digital integration of the flow signal (Gould waveform processor 160).

The pneumotachograph was calibrated directly for volume by injecting air from a gas syringe (Hans Rudolph Super 1.5 litre) and capturing the flow waveform using the digital oscilloscope. Volumes of 50–800 ml were injected manually in both directions through the tracheal tube and pneumotachograph assembly, and the flow waveform was integrated. The integrated volume, expressed in mV·s, was plotted against injected volume to yield a linear regression line ($r = 0.99$, $P < 0.0001$). The volumes injected varied between 162 ml and 1400 ml. Three of these samples were injected at the highest rate obtainable with the gas syringe, the remainder being injected over a 2-s period. When all the points were analysed, the standard deviation of the residuals from the regression line was 27.32 ml. With the three high flow points removed, the standard deviation of the residuals was 2.02 ml.

Experimental procedure

Each patient's lungs were ventilated at 0.8, 1.0, 1.2, 1.5, 2.0 and 2.5 Hz, and I:T ratios (ratio of inspiratory:total time) of 0.1, 0.3 and 0.5, in random order (a total of 18 measurements in each patient). The driving pressure of the jet gas was maintained at 1 bar (100 kPa). Each set of jet

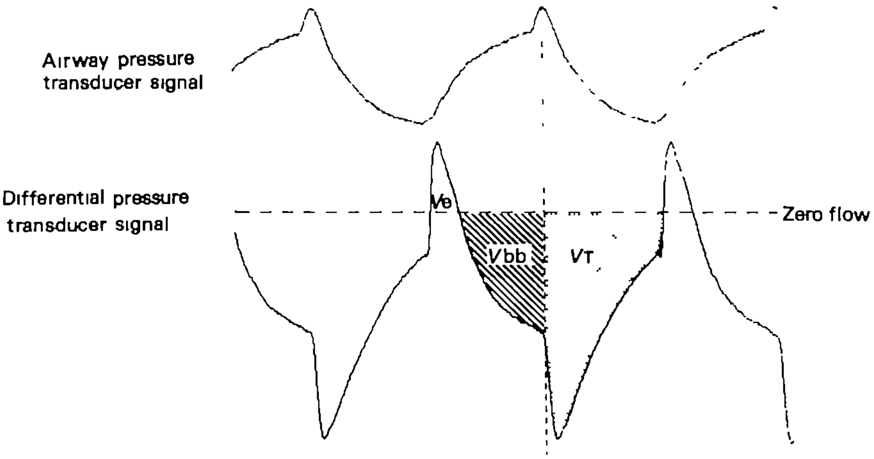

FIG. 2. Flow and airway pressure transducer signals over the ventilatory cycle. Flow into the lungs is defined as a positive deflection. Entrained, blowback and expired tidal volumes correspond to areas *V*e, *V*bb and *V*T, respectively. Small upward deflection at end of inspiration on pressure trace is an artefact caused by the ventilator pressure transducer line purge system.

parameters was maintained only long enough to obtain the physical measurements required, the ventilator then being re-set to a frequency and I:T ratio setting found to maintain good gas exchange ($f = 1.5$ Hz, I:T = 0.3). Pulse oximetry was observed at all times, and no clinically significant desaturations were noted.

For each frequency and I:T setting, the digital oscilloscope was set to capture eight or 16 cycles, depending on the degree of cardiac impulse artefact present, and an averaged waveform produced. This eliminated the superimposed flow waveform produced by cardiac impulses. The averaged waveform was divided digitally into three regions, which were integrated separately, as described below.

Measurement of gas volumes

Typical flow and airway pressure traces recorded by the oscilloscope are shown in figure 2. When the jet pulse begins, some of the gas passing through the bias flow tubing is entrained into the tracheal tube by momentum exchange. The inward flow of gas recorded by the pneumotachograph has been defined as a positive deflection. As airway pressure increases, further entrainment is opposed, and flow through the pneumotachograph ceases. The integral of the flow signal between the start of inspiration and the crossing of the zero flow line provides a measure of the gas entrained (*V*e).

During the remainder of inspiration, some of the jet gas is blown back directly into the bias flow without entering the lungs. Area *V*bb represents the integral of the measured flow from the point where entrainment ceases to the end of the jet pulse, indicated by the peak in airway pressure and a rapid change in the slope of the flow curve.

Finally, area *V*T is the outward passive flow during expiration, corresponding to tidal volume. The volume delivered by the jet may be calculated as follows:

$$V\text{jet} = V\text{T} + V\text{bb} - V\text{e}$$

RESULTS

Lung minute ventilation

Increases in the ventilation frequency from 0.8 to 2.5 Hz at constant I:T ratio induced an increase in minute ventilation, although this effect was smaller at small I:T ratios (fig. 3). Because the mean flow from the jet ventilator is the product of inspiratory flow and the I:T ratio, irrespective of frequency (Manufacturer's test data), this increase in minute ventilation must have resulted from either an increase in entrainment volume or a decrease in blowback volume.

Increasing the I:T ratio caused an increase in minute ventilation at any given frequency (fig. 3), although the volumes measured were less than predicted. For example, a change in I:T ratio from 0.1 to 0.3 represented an increase of 300% in inspiratory time fraction, whilst, at 2.5 Hz,

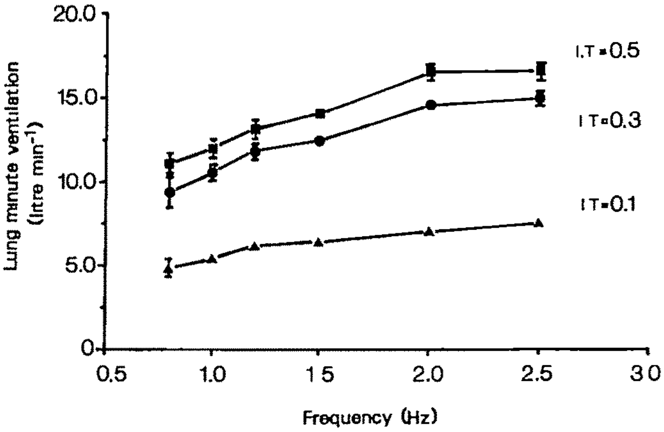

FIG. 3. Lung minute ventilation during HFJV at different ventilatory frequencies and I:T ratios (mean, SEM).

TABLE I. *Calculated tidal volumes (ml) at different ventilatory frequencies and I:T ratios*

Frequency (Hz)	I:T ratio		
	0.1	0.3	0.5
0.8	101	196	231
1.0	90	175	199
1.2	85	163	182
1.5	71	138	156
2.0	58	121	137
2.5	50	99	110

recorded mean minute ventilation increased by only 197 (SEM 2.4)%.

Calculated tidal volumes at different ventilatory frequencies and I:T ratios are shown in table I. As expected, tidal volume decreased with increasing frequency and increased with increasing I:T ratio.

Entrainment volume

The entrained minute ventilation increased with frequency at I:T ratios of 0.3 and 0.1 (fig. 4). However, a prolongation of fractional inspiratory time, by increasing I:T from 0.3 to 0.5 allowed "auto-PEEP" to develop, and restricted considerably the amount of gas entrained.

The calculated entrained volumes per insufflation (table II) were small and decreased with increasing I:T and ventilation frequency.

The contribution of entrainment to tidal volume was small, with a peak of approximately 20 % at low I:T, and it decreased to negligible amounts

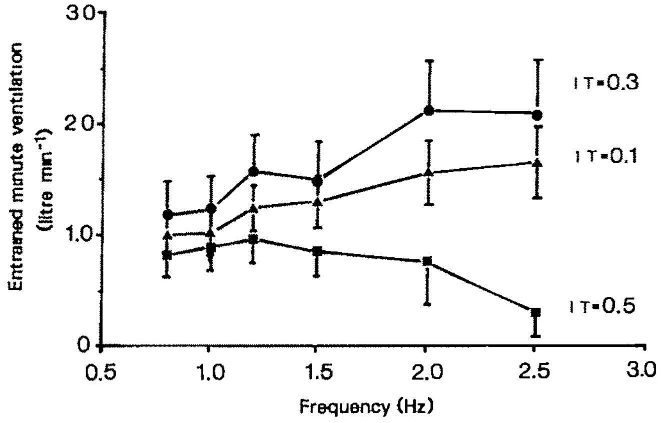

FIG. 4. Entrained minute volumes during HFJV at different ventilatory frequencies and I:T ratios (mean, SEM).

TABLE II. *Calculated entrained volumes (ml) per insufflation*

Frequency (Hz)	I:T ratio 0.1	0.3	0.5
0.8	21	25	17
1.0	17	21	15
1.2	17	22	13
1.5	14	17	9
2.0	13	18	6
2.5	11	14	2

TABLE III. *Blowback volumes (ml)*

Frequency (Hz)	I:T ratio 0.1	0.3	0.5
0.8	4	43	126
1.0	9	28	90
1.2	0	19	71
1.5	0	10	48
2.0	0	2	27
2.5	0	1	18

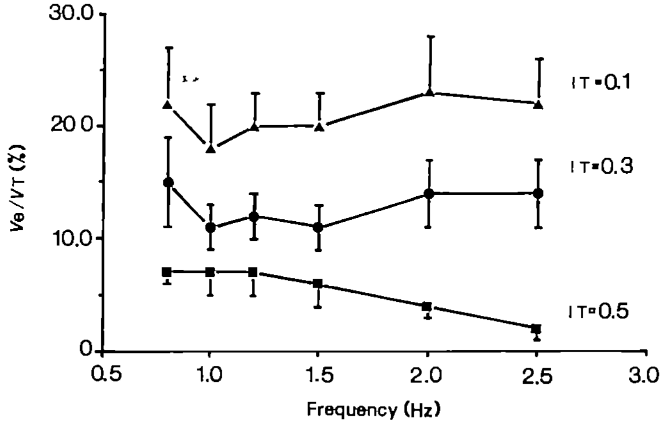

FIG. 5. Entrainment ratio (Ve/VT) during HFJV at different ventilatory frequencies and I:T ratios (mean, SEM).

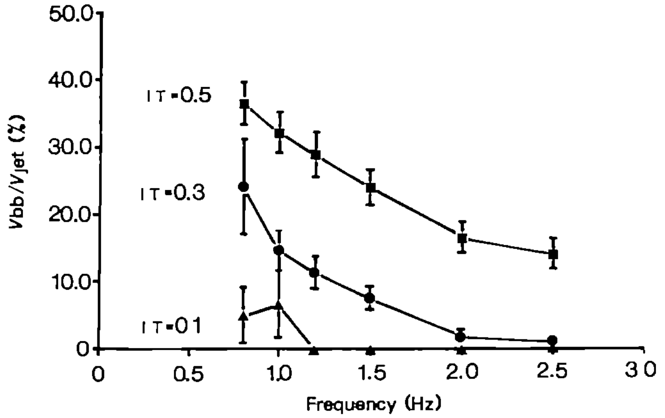

FIG. 6. Blowback volume expressed as a percentage of jet volume at different ventilatory frequencies and I:T ratios (mean, SEM).

as I:T and frequency increased (fig. 5). These conditions would be expected to increase airway pressure and so reduce the volume entrained.

Blowback volume

The volume of the jet pulse blown back into the bias flow decreased as ventilation frequency increased and was always minimal at low I:T ratios (table III). Measured as a proportion of the volume delivered by the jet pulse ($Vbb/Vjet$), the loss was large (30–40 %) at low frequencies with relatively long inspiratory times (fig. 6).

Generally, values for $\dot{V}$e, Vbb and V_T varied widely from subject to subject.

DISCUSSION

The method described here enables the gas volumes involved in HFJV to be measured in a clinical setting without the use of complex apparatus. This technique is similar to, but has some technical advantages over, the method developed independently by Young and Sykes, which has been applied in a lung model [6] and dogs [10]. In the present method, none of the background bias flow passes through the pneumotachograph, and so the only sources of error in the flow signal zero are amplifier and transducer drift. The method of Young and Sykes allows the whole of the bias flow to pass through the pneumotachograph, and so the "zero" output is susceptible to changes in the residual bias flow. As the separate ventilatory volumes are obtained by integration, it is important that zero values are maintained accurately.

In this paper the term "blowback" has been used in place of the word "spill" used by Young and Sykes, as it is felt that the former emphasizes the fact that this is an active phenomenon, occurring during the jet pulse.

Before examining the results obtained with this technique, it is necessary to examine the accuracy of the measurements. This study requires the pneumotachograph to operate at frequencies greater than the normal ventilatory frequency. The Fleisch head and pressure transducer combination used had a frequency response flat to 16 Hz. As the maximum ventilation frequency used was 2.5 Hz, and examination of the Fourier power spectra of jet drive pressure signals reveals negligible power at frequencies above the fourth harmonic [unpublished observations], the degree of error induced by the frequency response characteristics of the pneumotachograph should be minimal. The peak gas flows obtained in this technique (during passive expiration) were less than during normal tidal breathing, for which the transducer was designed, and so the measurements may be expected to fall within the linear range (0–160 litre min^{-1}).

We found that minute ventilation increased with frequency, despite a constant delivered volume from the ventilator. Consequently, the jet minute volume is not a useful guide in assessing the minute ventilation of the patient, as this does not take into account entrained and blowback volumes.

Entrainment is considered usually to be an important component of tidal volume. However, our results indicate that entrainment is quantitatively less important than has been suggested, at least with the commonly used insufflation system described. Entrainment ratio was optimal at an I:T of 0.1, any increase in percentage inspiratory time allowing a degree of "auto-PEEP" to develop and reducing the entrained volume to insignificant amounts.

The fraction of the inspired volume provided by entrainment remained relatively constant with frequency. Because the entrainment ratio was always low (usually 0.2 or less), and showed a wide inter-subject variation, it does not seem feasible to introduce volatile agents into the bias flow and produce predictable inspired concentrations. Minor changes in pulmonary mechanics (e.g. reduction in compliance, increase in airway resistance) may reduce or eliminate any contribution of entrainment. Similar conclusions were reached by Young and Sykes in studies using a model lung [6].

Blowback is a phenomenon occurring during the late part of the inspiratory period and is related to the interaction of the airway pressure and insufflation pressure of the body of gas accelerated by the entry of the jet. When the airway pressure exceeds the insufflation pressure, blowback occurs. Our study indicated that the loss of jet volume was substantial (30–40%) and influenced the tidal and minute volumes during HFJV. As the blowback volume was relatively large at lower frequencies, especially with increased I:T, this may be important in clinical practice, where the frequencies used most often are 1–2 Hz. The study by Tamsma and Spoelstra [11], using a canine model, supports this suggestion.

There was a wide variation in tidal, entrainment and blowback volumes between subjects under any given conditions, suggesting that the partitioning of the volume of gas delivered with each jet pulse (Vjet) into blowback volume (Vbb) and tidal volume (V_T) must be dependent on individual variations in airway and thoracic mechanics. It would be expected that subjects with a low thoracic compliance would reach the critical airway pressure, above which blowback occurs, at lower lung volumes than those achieved in normal subjects, thereby reducing tidal volume and increasing blowback volume. Thus the high frequency jet ventilator may act in a manner analogous to a pressure-cycled conventional ventilator under the conditions described.

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PLASMA CONCENTRATIONS OF METHADONE DURING POSTOPERATIVE PATIENT-CONTROLLED EXTRADURAL ANALGESIA†

Y. SHIR, D. EIMERL, F. MAGORA, D. DAMM, J. SCHULTE-MONTING AND J. CHRUBASIK

SUMMARY

Plasma concentrations of methadone were measured by gas chromatography in 16 patients receiving extradural methadone by continuous infusion for relief of postoperative pain. Venous blood samples were taken after a loading dose of extradural methadone 2 mg and during infusion of 0.46 mg h^{-1} plus patient-controlled increments of 0.2–1 mg. Mean (SD) plasma concentration of methadone was 9.8 (2.1) ng ml^{-1} at 15 min; this did not change significantly during the first 2 h, after which it increased gradually to 32.2 (4.6) ng ml^{-1} ($P < 0.001$) at the end of 24 h. The mean quantity of extradural methadone required to produce effective analgesia was 10.3 (1.8) mg during the first 12 h after operation and 6 (1.0) mg for the subsequent 12 h. The mean amount of methadone for effective analgesia on the second day was 7.6 (1.1) mg. No adverse effects were detected during the 2–3 days of methadone therapy. Plasma concentration of methadone increased significantly during patient-controlled infusion of extradural methadone in the first 24 h after operation, suggesting rapid vascular uptake. Systemic activity of the drug contributes to the analgesic effect of extradural methadone.

KEY WORDS

Analgesics, opioid: methadone. Analgesia: patient-controlled. Analgesic techniques: extradural. Methadone.

Many investigators have examined the pharmacokinetics and analgesic effects of extradural injections of opioids [1–4]. Studies on vascular absorption of opioids such as pethidine [5] and fentanyl [6] have demonstrated that a major portion is absorbed initially by direct vascular absorption from the extradural space, followed by uptake from CSF.

Until 1987 [7], there have been no studies of the plasma concentrations of methadone produced by extradural administration in bolus dose or continuous infusion. The extent of systemic uptake is influenced mainly by lipid solubility [8, 9]. Methadone has a much higher lipid partition coefficient than morphine (116 *vs* 1.42) and therefore has more rapid onset of action, with less likelihood of delayed respiratory depression [10]. It has been shown that methadone has a potency similar to that of morphine; it produces effective analgesia following extradural administration, but with fewer side effects [11–13]. Its lack of urinary complications makes it particularly suitable for postoperative analgesia [13]. However, rapid vascular absorption in combination with slow plasma clearance [14, 15] may result in systemic cumulation after repeated extradural injections or continuous extradural infusion.

The present study was designed to assess the safety of continuous extradural infusion of methadone, by measurement of plasma concentrations

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TABLE I. *Patient data*

Patient No.	Age (yr)	Sex	Surgical procedure
1	58	F	Hemicolectomy
2	60	F	Mid sternotomy
3	28	M	Colonic surgery
4	26	M	Vagotomy pyloroplasty
5	61	M	Abdomino-perineal resection
6	81	M	Choledochojejunostomy
7	56	F	Abdomino-perineal resection
8	64	M	Abdomino-perineal resection
9	73	M	Aorto-bifemoral bypass
10	75	M	Cholecystectomy
11	58	F	Cholecystectomy
12	66	M	Resection of abdominal aortic aneurysm
13	53	F	Cholecystectomy
14	46	F	Hemicolectomy
15	64	M	Radical cystectomy
16	54	F	Hemicolectomy

of methadone during its use in postoperative patient-controlled analgesia.

PATIENTS AND METHODS

We studied 16 patients (seven women) aged 26–75 yr, undergoing major elective abdominal or thoracic surgery (table I). All patients gave informed consent to the study, which was approved by the local Ethics Committee. All patients received general anaesthesia; premedication and anaesthetic technique were not standardized, but included supplementation with low doses of fentanyl 1–2 mg kg^{-1} i.v. After induction of anaesthesia, a catheter was inserted 2.5 cm into the extradural space via an upper lumbar interspace for administration of methadone.

On completion of surgery, a loading dose of 0.1% racemic methadone hydrochloride 2 mg in 10% glucose was injected through the extradural catheter, which was connected to a 5-ml plastic syringe containing methadone. The syringe was driven by an automatic, portable, battery-operated infusion pump (Graseby, Medical M 26, England). The rate of infusion was set to deliver methadone 0.46 mg h^{-1} for the first 24 h after surgery, after which it was reduced to 0.35 mg h^{-1}. For the first 2 h, repeated doses of methadone to a total of 6 mg were administered by the investigator if the patient reported severe pain. Thereafter, the patients and the nursing staff were instructed not to allow the pain to increase above a level of 3 (see below), and to add further boluses of 0.2–1.0 ml solution if pain relief was inadequate. The syringe was refilled by the nurse according to the regimen, which permitted additions of methadone up to 5 mg every 6 h. Escape analgesia was provided by systemic opioids.

The amount of methadone required for good analgesia was calculated separately for the first two 12-h epochs and the second day after operation. The patients were observed in the recovery room during the study period and ventilation was monitored at frequent intervals; blood-gas tensions were measured 1 h after surgery and at least twice daily thereafter.

Analgesic efficacy was assessed by a subjective five-point pain score (0 = no pain; 1, 2 = mild pain; 3 = discomforting pain; 4 = distressing pain; 5 = unbearable pain, intervals 0.5). During the first 3 h of administration of methadone, the pain score was assessed every 30 min by one of the investigators, who collected blood samples and administered additional analgesia if necessary. For the remainder of the observation period, the average of frequent score assessments (every 1 h for the first 12 h, every 4 h for the remainder of the study period) was calculated for the first and second days after surgery. These two scores were used for statistical evaluation.

Central venous blood samples were collected in heparinized tubes before and at 15, 30, 45, 60 min and 2, 3, 4, 6, 8, 12 and 24 h after the first dose of extradural methadone. The blood was centrifuged and the plasma samples were frozen and transported to Frankfurt (W. Germany) for analysis. Plasma concentrations of methadone were measured by gas chromatography using a Hewlett–Packard 5730 apparatus with a nitrogen phosphorus detector and a Spectra Physics model SP 4270 integrator [16]. This assay is sensitive to concentrations of less than 1 ng ml^{-1} in plasma samples as small as 1 ml. The extraction procedure for methadone as modified by one of the authors (J. S.-M.) utilizes acid–base partitioning steps which allow a large number of samples to be processed rapidly. The coefficient of variation was 3.5–22% over a concentration range of methadone 1–50 ng ml^{-1}. The technique was linear up to 200 ng ml^{-1} [7].

Linear least square regression was used for statistical analysis of plasma concentrations of methadone. Mean analgesic requirements for methadone and patients' pain scores were

TABLE II. *Individual methadone consumption and pain scores during the first 2 days after surgery*

Patient No.	Methadone consumption (mg) 1st day	Methadone consumption (mg) 2nd day	Pain score 1st day	Pain score 2nd day	Remarks
1	18	6	0	0	
2	17	9	2	0	
3	15	8	1	1	Post-op. intubation: 4 h
4	19	8	3	0	Papaveretum 10 mg i.m.
5	16	7	2	2	Post-op. intubation: 10 h
6	16	5	0	0	
7	19	8	3	1	Papaveretum 10 mg i.m.
8	17	8	2	0	Post-op. intubation: 5 h
9	15	9	1	0	Post-op. intubation: 12 h
10	15	7	2	1	Urinary retention
11	13	7	0	0	
12	13	7	1	2	Post-op intubation: 6 h
13	17	7	2	2	
14	18	8	1	1	
15	17	9	1	0	
16	16	7	0	0	
Mean (SD)	16.3 (1.8)	7.6 (1.1)	1.3 (1)	0.6 (0.8)	
P	< 0.05		< 0.05		

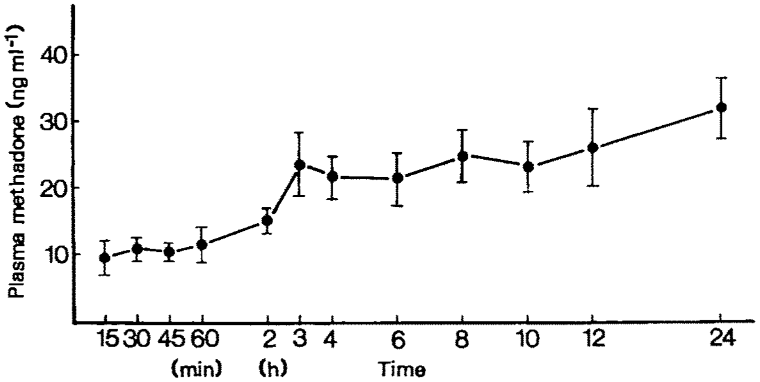

FIG. 1. Mean plasma concentration of methadone during the first 24 h after operation, with continuous patient-controlled extradural infusion of methadone.

analysed by paired Student's *t* test. $P < 0.05$ was considered significant.

RESULTS

The mean amount of methadone consumed during the first day was 16.3 (SD 1.8) mg (range 13–19 mg) (table II). During the first 12 h, mean consumption of methadone was 10.3 (1.8) mg, whereas during the next 12 h of treatment a mean of only 6 (1.0) mg provided analgesia ($P < 0.05$). As the rate of injection was set at 5 mg/11 h, the doses used indicate substantial need for supplementary methadone during the first postoperative period, with little or no supplement during the second 12 h. Onset of analgesia was rapid: 5–10 min after bolus injection, either self-administered or given by the nurse. On the second day, significantly smaller quantities of extradural methadone were needed, with a mean value of 7.6 (1.1) mg (range 5–9 mg) ($P < 0.05$). During these two days, the pain scores were 1.3 (1) and 0.6 (0.8), respectively ($P < 0.05$). Two patients who reached the prescribed limits of extradural methadone in the first hours following surgery, had a pain score of 3, 15 min after supplementation with methadone, and received papaveretum 10 mg i.m.

In five patients, artificial ventilation was continued for 4–12 h after surgery. Otherwise,

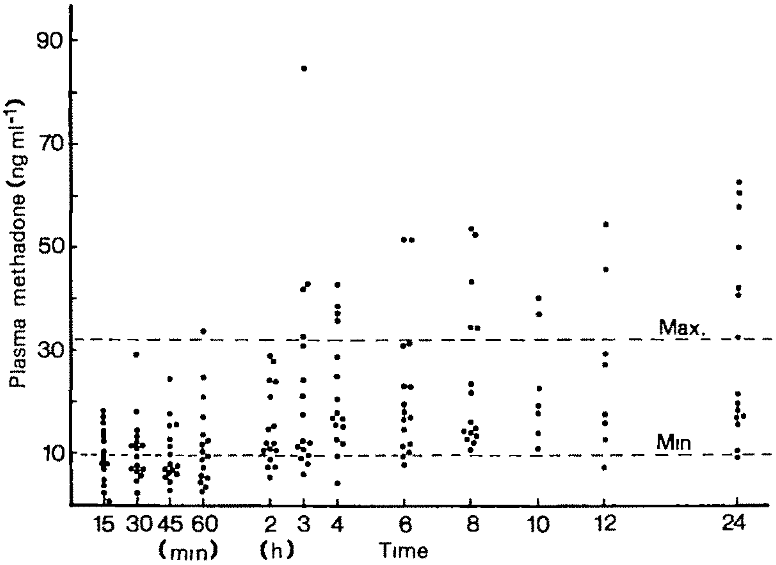

FIG. 2. Individual plasma concentrations of methadone during the first 24 h after operation, with continuous patient-controlled extradural infusion of methadone. Min. = Mean minimum plasma concentration of methadone in the 16 patients studied, after 15 min; Max. = mean maximum plasma concentration of methadone in the 16 patients studied, after 24 h.

there were no respiratory complications or marked deviation from normal values in blood-gas tensions.

Plasma concentrations of methadone

Mean plasma concentrations of methadone during continuous infusion with on-demand supplementation in the first 24 h after operation are shown in figure 1. Fifteen minutes after the loading dose of extradural methadone 2 mg and subsequent continuous infusion, the plasma concentration of methadone was 9.8 (2.3) ng ml^{-1}. The value after 60 min was not significantly different (11.9 (2.1) ng ml^{-1}). After the first 1 h, plasma concentration of methadone increased gradually, to mean values of 14.9 (2.8) ng ml^{-1} at 2 h, 21.9 (2.8) ng ml^{-1} at 3 h and 32.2 (4.6) ng ml^{-1} 24 h after operation. Regression analysis showed a significant increase in plasma concentrations of methadone with time, with peak values at the 2 h ($P < 0.05$), 3 h ($P < 0.05$) and 24 h ($P < 0.001$) of extradural infusion of methadone.

Methadone concentrations varied considerably between individuals (fig. 2), although the general trend towards increased concentrations was similar in all patients. On several occasions, high values were recorded in some patients, which corresponded with additional boluses. Although most patients were sleepy during the first few hours after operation, all, including those receiving artificial ventilation, were fully conscious and co-operative. No respiratory depression, haemodynamic instability or neurological changes were observed in any patient. None exhibited signs of atelectasis on the chest x-ray taken the morning following the operation. One of the seven patients without a urinary catheter required temporary catherization of the bladder.

DISCUSSION

This study has shown that postoperative pain associated with major abdominal and thoracic surgery was controlled effectively by continuous lumbar extradural administration of methadone. Intermittent extradural administration of bolus doses of methadone has been reported to produce good analgesia after surgery [11, 13, 17] and extracorporeal shock wave lithotripsy [18]. Extradural methadone 8–12 mg day^{-1} has been reported to give good analgesia for several weeks without toxic effects in patients with chronic pain [19].

The prescribed dose limit of extradural infusion of methadone plus on-demand boluses of up to

5 mg every 6 h was based on other studies and our own previous experience [7, 12, 13, 18, 19]. The mean consumption of methadone in 24 h of our patients was less than the total amount given in bolus injections during the same period after thoracic surgery [17], but greater than the single doses recommended after lower abdominal surgery [13].

Lipophilic opioids are taken up more readily from the extradural space and, therefore, are less likely to cause late respiratory depression than lipophobic drugs. Payne and Inturrisi [10] could not detect methadone in the cisternal CSF of sheep up to 6 h after injection of methadone 2 mg into the lumbar subarachnoid space. In contrast, subarachnoid injection of the same dose of morphine resulted in a concentration of morphine 148 ng ml^{-1} in the cisterna magna, after only 2–3 h. The authors concluded that methadone, as opposed to the hydrophilic morphine, was taken up almost completely into the cord. This concept is supported by previous studies of extradural methadone and the present investigation, in which no central side effects were observed. Continuous infusion of methadone supplemented by patient-controlled boluses prevented onset of severe pain; however, its high lipophilicity leads to rapid vascular absorption. In addition, methadone possesses a long plasma terminal half-life—more than 24 h [20, 21], and this may lead to cumulation during prolonged continuous infusion. The present study has confirmed that methadone passed rapidly into the circulation, as demonstrated by the plasma concentration at 15 min. The relatively constant plasma concentration observed during the first 1 h of continuous infusion may be a reflection of its rapid phase of distribution—6.1 (5.7) min [20]. The significant increase in the subsequent 3 h may have been related either to the kinetics of extradural methadone, or to the increments necessary to treat immediate severe postoperative pain. The slow increase towards the peak concentration of 32.2 ng ml^{-1} at 24 h reflects the long terminal half-life. However, the mean 24 h value was below the minimal analgesic blood concentration (57.9 ng ml^{-1}) reported by Gourlay, Willis and Wilson after i.v. administration [22]. Although high plasma concentrations of methadone were observed occasionally, none reached a toxic value, and there was no clinical evidence of toxicity during the 3 days of treatment.

The good quality of analgesia in the early postoperative period, when blood concentrations were low, is consistent with a spinal site of action of the drug. Because of this increasing blood concentration of methadone, observed during the 24 h of investigation, it would be advisable to reduce the rate of infusion until further studies are performed.

It is concluded that the amounts of methadone infused continuously after upper abdominal and thoracic surgery resulted in satisfactory pain relief; no sign of toxic effects was observed during the study, and the range of plasma concentrations of methadone during the first 24 h remained in the non-toxic range.

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EFFECTS OF NITROUS OXIDE ON CEREBRAL METABOLIC RATE IN RATS ANAESTHETIZED WITH ISOFLURANE†

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SUMMARY

It has been demonstrated in several species that a significant increase in cerebral blood flow (CBF) occurs when nitrous oxide is added to a volatile anaesthetic. This blood flow response could result from an increase in cerebral metabolic rate or from a direct effect of nitrous oxide on cerebral vessels. To investigate this, the cerebral metabolic rate for glucose (CMRglu) was determined autoradiographically in rats receiving isoflurane anaesthesia with or without nitrous oxide. An increase in anaesthetic depth from 0.5 to 1.0 MAC achieved with isoflurane alone caused a significant reduction in CMRglu (52 (SD 11) μmol/100 g min^{-1} vs 39 (8) μmol/100 g min^{-1}). In contrast, the addition of 70% nitrous oxide (0.5 MAC) to 0.5 MAC isoflurane anaesthesia (1 MAC total) left CMRglu unchanged (54 (4) μmol/100 g min^{-1}). We conclude that 70% nitrous oxide does not alter cerebral metabolic rate when administered with 0.5 MAC isoflurane. Because CBF increases substantially under very similar conditions, our data indicate that the CBF effects of nitrous oxide, when administered with a volatile agent, were direct and mediated by factors other than changes in cerebral metabolic rate.

KEY WORDS

Anaesthetics gases: nitrous oxide. Anaesthetics volatile isoflurane. Brain. cerebral metabolic rate.

Nitrous oxide may cause substantial increases in cerebral blood flow (CBF) [1, 2]. Our laboratory recently confirmed that this is particularly evident if nitrous oxide is administered in combination with a volatile anaesthetic. For example, CBF in the normocapnic rat is about 50% greater when an anaesthetic depth of 1 MAC is achieved with a combination of isoflurane and nitrous oxide than with 1 MAC isoflurane alone [3].

One possible explanation for the synergistic effects on CBF of nitrous oxide and isoflurane may lie in the net effect of this combination of anaesthetic agents on cerebral metabolism. Several pieces of evidence are consistent with this hypothesis. First, CBF and metabolism have been shown to be interrelated closely in both the awake [4–6] and anaesthetized states [5, 7]. Furthermore, isoflurane depresses cerebral metabolic rate (CMR) in a dose-dependent manner [8] of magnitude similar to that observed for the barbiturates [9]. However, when nitrous oxide is added to a light pentobarbitone anaesthetic, CMR is increased by 40–50% in the rat [10]. If a similar antagonism of isoflurane-induced depression of CMR were caused also by nitrous oxide, flow might be expected to increase in a near parallel manner. Alternatively, nitrous oxide may have little effect on CMR [11] and act only as a direct cerebral vasodilator. To test this hypothesis, we have determined autoradiographically the cerebral metabolic rate for glucose (CMRglu) in rats anaesthetized with isoflurane alone (0.5 or 1.0 MAC) and have compared the data with those obtained from rats receiving a 1 MAC combination of nitrous oxide–isoflurane.

MATERIALS AND METHODS

This study was approved by the University of Iowa Animal Care and Use Committee. Twenty-

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one male Sprague–Dawley rats weighing 310–390 g were anaesthetized with 2 % isoflurane with 33 % oxygen in nitrogen. A tracheotomy was performed and the animal connected to a mechanical ventilator with a tidal volume of 2.5 ml and a ventilatory frequency of 60 b.p.m. Femoral arterial and venous catheters, and a tail artery catheter, were inserted via surgical incisions, and all wounds were infiltrated with 2.0 % lignocaine. The tail artery catheter was connected to a transducer for continuous monitoring of arterial pressure. The femoral arterial catheter was used for blood sampling, while the venous catheter was used for administration of drugs and fluids. Heparin 200 iu and tubocurarine 2 mg were administered i.v. to each rat. A surgical preparation interval of 35 min was allowed (measured from the start of anaesthesia induction).

Following surgical preparation, rats were allocated randomly to one of three groups: group 1 = 0.5 MAC isoflurane (0.7 %) and 70 % nitrogen in oxygen; group 2 = 1 MAC isoflurane (1.4 %) and 70 % nitrogen in oxygen; group 3 = 0.7 % isoflurane and 70 % nitrous oxide in oxygen (0.5 MAC isoflurane + 0.5 MAC nitrous oxide). The respiratory gas mixture was adjusted accordingly, with measurement of gas concentrations made in the expiratory limb of the anaesthesia circuit with a Puritan Bennet Datex Model 222 Anesthetic Agent Analyzer and a Foregger oxygen analyser. MAC values in the Sprague–Dawley rat for isoflurane and nitrous oxide were taken respectively from White, Johnston and Eger [12] and Difazio and colleagues [13]. The rats remained anaesthetized an additional 35 min before measurement of CMRglu was started. During this equilibration period, the ventilator was adjusted to maintain normoxia (Pa_{O_2} 14.6–18.6 kPa) and normocapnia (Pa_{CO_2} 4.8–5.2 kPa). Body temperature was monitored via a rectal probe and maintained at 36.8–37.2 °C by surface heating or cooling. Mean arterial pressure (MAP) was monitored continuously and maintained within the range 95–105 mm Hg throughout the remainder of the experiment by infusion of donor rat blood as required.

Determination of CMRglu

Thirty-five minutes after the end of surgery, arterial blood-gas values were recorded and ^{14}C-2-deoxyglucose (^{14}C-2-DG) (specific activity 50–56 mCi mmol^{-1}, New England Nuclear, Boston) 100 μCi kg^{-1} was infused i.v. at a constant rate over 30 s via an infusion pump. Fourteen 100-μl arterial samples were collected at defined intervals over the next 45 min. Samples were centrifuged immediately and the plasma saved for later determination of carbon-14 activity and glucose concentration. The animals were then decapitated and the brains removed rapidly and frozen in 2-methylbutane (−50 °C). Twenty microlitre of each timed arterial plasma sample was placed on chromatography paper and dried for 24 h, then eluted for 24 h in water 1 ml and liquid scintillation mixture 9 ml (Ready-Solv HP/b, Beckman Fullerton). Radioactivity was determined by liquid scintillation counting (Searle, Model 6880, Des Plaines) using an external quench correction. Plasma glucose concentrations were measured by the glucose oxidase method (YSI Model 27, Yellow Springs).

Autoradiography and image analysis

Frozen brains were cut into 20-μm thick serial coronal sections on a cryostat (−20 °C). Quadruplicate sections taken at 240-μm intervals were mounted on glass slides, dried for 5 min on a hot plate (50 °C), and exposed to autoradiographic film (Kodak SB-5) for 5–8 days with seven ^{14}C-methylmethacrylate standards (Amersham, Arlington Hts). Images of eight standardized brain sections from each animal were chosen for further analysis based on anatomical landmarks over the rostral–caudal axis [14]. These landmarks were precisely the same as those used in our previous CBF publication relating to this subject [3]. These images were converted to digitized optical density images on a scanning microdensitometer system (Eikonix-Kodak, Bedford) with a camera aperture of 100 μm and a fixed focal length. Optical densities from these autoradiographic images, radioactivity values from the carbon-14 standards, and timed arterial blood radioactivity and glucose values were entered into a digital Micro-Vax computer system. Recalculation of CMRglu values from brain images utilized the equations developed by Sokoloff and colleagues [15] (lumped constant = 0.483), with mathematical operations performed using a quantitative glucose utilization program (A. Toga, Washington Univ., St. Louis).

Data analysis

Digitized CMRglu images were pseudo-colour enhanced and displayed on a cathode ray screen.

Regions of interest were circumscribed using an operator controlled cursor. Mean CMRglu values and area (in pixel units) were recorded for each region. Primary regions of interest in each section were hemisphere, neocortex and subcortex, where the subcortex was defined as the total hemispheric area minus the area of the neocortical mantel [14]. These regions of interest were chosen to correspond directly to those regions of interest utilized in our related CBF study [3]. Olfactory cortex was included in the subcortex, as it is considered a limbic structure. "Whole brain" values for hemispheric, neocortical and subcortical CMRglu were determined as area-weighted averages of values from each of the eight sections in each rat. Physiological values and CMRglu values for each region of interest were compared between anaesthetic groups by one-way analysis of variance. *Post hoc* comparisons for specific between group differences were performed with the Newman–Keuls *t* test when indicated by a significant *F* ratio. CMRglu values are reported as mean (SD) with significance assumed when $P < 0.05$.

RESULTS

Physiological values recorded immediately before determination of CMRglu are given in table I. No differences were observed between anaesthetic groups for arterial pH, Pa_{CO_2}, Pa_{O_2}, plasma glucose concentration, mean arterial pressure, or rectal temperature. MAP remained at 95–105 mm Hg throughout the 45-min ^{14}C-2-DG uptake interval while the volume of blood infused to maintain haemodynamic stability did not differ significantly between groups.

Table II summarizes the mean area-weighted CMRglu values for the three major tissue regions for each anaesthetic group. In the hemispheric, neocortical and subcortical regions of interest, CMRglu values were reduced by 20–25 % in the 1 MAC isoflurane group compared with the 0.5 MAC isoflurane group ($P < 0.05$). In contrast, when 1 MAC depth of anaesthesia was achieved instead by adding 70 % nitrous oxide to 0.5 MAC isoflurane, CMRglu values were not different from those obtained in animals receiving 0.5 MAC isoflurane alone. Values from the nitrous oxide + isoflurane group were also greater than those observed in the 1.0 MAC isoflurane group ($P < 0.05$).

TABLE I. *Physiological values (mean* (SD)) *measured immediately before determination of CMRglu as a function of anaesthetic regimen. No significant differences between groups. Iso. = isoflurane*

	0.5 MAC Iso.	1.0 MAC Iso.	0.5 MAC N_2O + 0.5 MAC Iso.
n	7	7	7
Weight (g)	340 (45)	319 (40)	353 (27)
pH	7.42 (0.02)	7.40 (0.02)	7.42 (0.02)
Pa_{CO_2} (kPa)	5.0 (0.1)	4.9 (0.1)	5.0 (0.2)
Pa_{O_2} (kPa)	15.7 (2.5)	16.4 (1.6)	16.8 (2.1)
Total blood infused (ml)	3.9 (0.6)	4.3 (0.9)	3.1 (1.1)
MAP (mm Hg)	104 (3)	103 (2)	104 (3)
Glucose (mg dl^{-1})	163 (45)	147 (38)	179 (45)

TABLE II. *CMRglu values (mean* (SD)) *in hemispheric, neocortical and subcortical regions for each anaesthetic group presented as area-weighted average values over eight coronal sections.* * *Significant difference* ($P < 0.05$) *between 1.0 MAC isoflurane vs 0.5 MAC isoflurane or 0.5 MAC isoflurane + 70 % N_2O in the respective regions*

	CMRglu (μmol/100 g min^{-1})		
Anaesthetic	Hemisphere	Neocortex	Subcortex
0.5 MAC Isoflurane	48 (10)	52 (11)	46 (10)
1.0 MAC Isoflurane	37 (8)*	39 (8)*	37 (8)*
0.5 MAC Isoflurane + 70 % nitrous oxide	52 (4)	54 (4)	51 (4)

DISCUSSION

The purpose of this investigation was to determine the effect of nitrous oxide on cerebral metabolic rate when administered in combination with a light (0.5 MAC) isoflurane anaesthetic. While the methodology utilized in this experiment was sensitive enough to identify a depression in metabolic rate if the depth of anaesthesia was increased from 0.5 to 1.0 MAC with isoflurane, no change in CMRglu was observed when the same depth of anaesthesia was achieved instead by adding 70% (0.5 MAC) nitrous oxide.

This absence of a significant effect of nitrous oxide on CMRglu, when administered with 0.5 MAC isoflurane, is in contrast with the profound effect of nitrous oxide on CBF under physiologically comparable circumstances (fig. 1). As noted above, we recently reported that a 1 MAC combination of nitrous oxide–isoflurane resulted in a 55% increase in global CBF compared with 0.5 MAC of isoflurane alone [3]. As CMRglu did not change in the current study (under identical circumstances), it may be concluded that the increase in CBF caused by nitrous oxide when administered with a volatile agent was not caused by activation of cerebral metabolism causing a coupled increase in blood flow.

While there is considerable agreement that the addition of nitrous oxide to a volatile anaesthetic resulted in an increase in CBF [1,3,16–20], less information is available for comparison concerning the changes in CMR. Sakabe and colleagues measured the jugular arterial–venous oxygen content difference in four patients who were receiving an end-tidal halothane concentration of 0.84% and 60% nitrogen in oxygen [21]. The reciprocal of this gradient was calculated to provide an estimate of the ratio CBF:CMR. When nitrous oxide was substituted for nitrogen, the CBF:CMR ratio increased significantly in all four patients. However, because CBF and CMR were not determined independently, it is not known whether CBF increased alone, if CMR decreased alone, or if both CBF and CMR varied. In a later experiment in the rabbit, Kaieda, Todd and Warner examined the CBF and CMR effects of nitrous oxide when added to a 1 MAC background of either isoflurane or halothane during both normo- and hypocapnia. In all cases nitrous oxide caused a significant increase in blood flow but no change in metabolism [20]. The only potential criticism of that study is that the calculation of CMR (i.e. CBF × $(Ca_{O_2} - Cv_{O_2})$) was not independent of CBF.

Other studies designed to evaluate the combined effects of nitrous oxide and volatile anaesthetics on CMR have been performed in the dog. For example, Sakabe and colleagues have reported that, 10 min after 60% nitrous oxide was added to a background anaesthetic of 0.2% halothane, CBF increased by 107% while CMR (again calculated as CBF × $(Ca_{O_2} - Cv_{O_2})$) in-

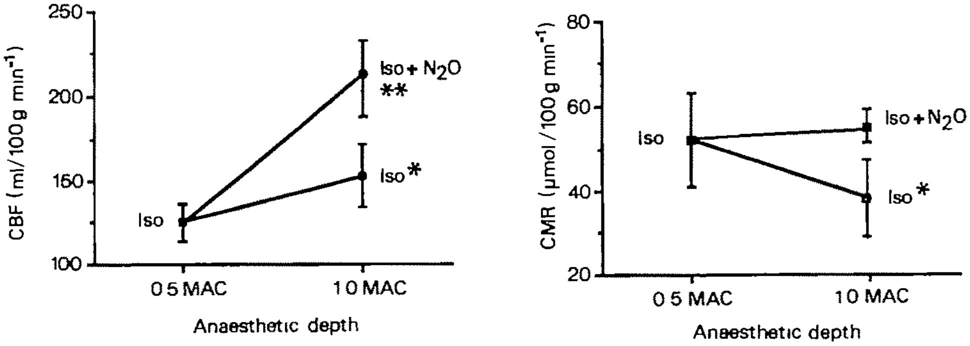

FIG. 1. Left: Area-weighted blood flow values (mean, SD) in the neocortex as a function of anaesthetic depth. $^{**}P < 0.01$ comparing blood flow during exposure to 1 MAC isoflurane with 0.5 MAC isoflurane or a 1-MAC combination of nitrous oxide–isoflurane; $^{*}P < 0.05$ comparing 1 MAC isoflurane with 0.5 MAC isoflurane. (CBF data reported previously by Hansen and colleagues, derived under essentially identical experimental conditions as described for the determinations of CMRglu [3].) Right: Area-weighted CMRglu values (mean, SD) in the neocortex as a function of anaesthetic depth. $^{*}P < 0.05$ comparing CMRglu during exposure to 1 MAC isoflurane with 0.5 MAC isoflurane alone or a 1-MAC combination of nitrous oxide–isoflurane. There was no difference between 0.5 MAC isoflurane and a 1-MAC combination of nitrous oxide–isoflurane.

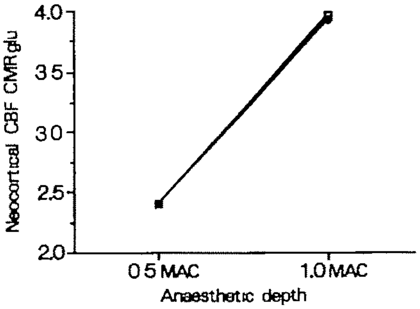

FIG. 2. Neocortical CBF:CMRglu ratios as a function of anaesthetic depth for the three anaesthetic groups. The ratios were computed using the mean values from groups of seven animals each wherein either CBF or CMRglu were determined. CBF values are taken from those previously reported by Hansen and colleagues [3]. □ = Isoflurane + nitrous oxide; ◆ = isoflurane.

creased by only 16%. If, instead, the halothane concentration was first stabilized at 0.8%, the addition of nitrous oxide caused a 65% increase in CBF while CMR remained unchanged [1]. Thus, while the effect of nitrous oxide on CMR may be substantial when compared with near awake or awake values [2], the same agent has little or no effect on CMR when added to at least 0.5 MAC volatile agent.

We believe that the CBF effect of nitrous oxide, when administered with a background volatile agent is explained best by a direct vasodilator action of the drug on cerebral vessels. Several pieces of evidence are consistent with this interpretation. First, if we assume that blood flow and metabolism in the brain remain linearly related (i.e. coupled) during intermediate levels of anaesthesia (which has been demonstrated for barbiturates, halothane and isoflurane [7, 15]), it should be possible to control for any metabolic contribution of an agent to the regulation of CBF by inspecting the ratio of CBF:CMR values determined under identical anaesthetic and physiological circumstances. We have performed this calculation on the mean neocortical CMRglu values obtained in the present study, together with the mean neocortical CBF values reported recently by Hansen and colleagues [3]. This calculation yields a CBF:CMRglu ratio of 3.96 during 1 MAC nitrous oxide–isoflurane anaesthesia (CBF = 214 ml/100 g min^{-1}; CMRglu = 54 μmol/100 g min^{-1}), which is nearly identical to the ratio of 3.92 observed during 1 MAC isoflurane alone (CBF = 153 ml/100 g min^{-1}; CMRglu = 39 μmol/100 g min^{-1}). In contrast, for 0.5 MAC isoflurane (CBF = 125 ml/100 g min^{-1}; CMRglu = 52 μmol/100 g min^{-1}) a value of 2.40 was calculated (fig. 2). Thus the flow:metabolism ratio appears to be influenced more by depth of anaesthesia than by the presence or absence of nitrous oxide. It is more likely, therefore, that nitrous oxide causes a shift in the CBF:CMR ratio by contributing a direct vasodilator effect to the overall balance which is similar in magnitude to that provided by the addition of 0.5 MAC isoflurane. In contrast to isoflurane, however, the vasodilator effect of nitrous oxide is not modulated by a concomitant reduction in CMR and hence the resultant flows are greater.

There is one final piece of evidence supporting the conclusion that the effects of nitrous oxide on CBF are CMR independent. We have studied the effects of nitrous oxide on the EEG changes in rats undergoing progressively severe unilateral hemispheric hypoperfusion [22]. The MAP at which EEG slowed was found to be independent of the presence or absence of nitrous oxide, but it was related to the concentration of volatile anaesthetic. If nitrous oxide produced a significant increase in CMR during halothane anaesthesia, one would expect that the brain would be less tolerant of a reduction in CBF when nitrous oxide was present. The absence of such an effect mitigates against a significant metabolic effect of nitrous oxide during volatile anaesthesia.

Included in the theoretical basis for this experiment, was the observation made by Sakabe and colleagues that nitrous oxide does increase CMRglu when added to a light (but not deep) pentobarbitone anaesthetic [10]. The CMRglu interaction between nitrous oxide and barbiturates is therefore different from that observed for nitrous oxide and isoflurane. We can only speculate on the mechanism of this effect. Both isoflurane and barbiturates decrease CMR in a dose-dependent manner, and to a similar degree [8, 9]. Because the end-point for CMR reduction for both agents is EEG isoelectricity, a common mechanism of action which mediates CMR reduction is suggested. However, the observed differential effects of nitrous oxide on CMRglu, when administered with isoflurane in comparison with pentobarbitone, may indicate that while the end-point for CMR reduction is similar for the two agents, the mechanism by which EEG suppression occurs is not.

In summary, it has been observed previously that CBF is greater when 1 MAC anaesthetic depth is achieved by a combination of isoflurane and nitrous oxide than when isoflurane is used alone. When the same anaesthetic conditions were repeated in this study CMR was unaffected by nitrous oxide. This evidence speaks strongly against the hypothesis that the CBF effects of nitrous oxide, when administered with a volatile agent, are caused by metabolic activation of the brain and a coupled increase in CBF. In contrast, the data presented here are consistent with the conclusion that nitrous oxide is a potent direct cerebrovasodilator.

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I.V. LIGNOCAINE FAILS TO ATTENUATE THE CARDIOVASCULAR RESPONSE TO LARYNGOSCOPY AND TRACHEAL INTUBATION

C. D. MILLER AND S. J. WARREN

SUMMARY

I.v. lignocaine has been used with varying success to attenuate the cardiovascular responses to laryngoscopy and tracheal intubation. We determined the optimal time of administration in 45 ASA I and II Chinese patients premedicated with morphine and hyoscine, and anaesthetized with thiopentone and suxamethonium. Patients were allocated randomly to a control group or three treatment groups to receive lignocaine 1.5 mg kg^{-1} i.v. 1, 2, or 3 min before laryngoscopy. Analysis of variance for measured and derived cardiovascular variables failed to show any significant difference between any of the groups.

KEY WORDS

Intubation, tracheal lignocaine, cardiovascular responses. Anaesthetics, local · lignocaine

The increase in arterial pressure and heart rate caused by laryngoscopy was first described 38 years ago [1]. This response is potentially harmful in patients with cardiac disease or increased intracranial pressure.

In an attempt to attenuate this response, various manoeuvres have been recommended, including pretreatment with i.v. lignocaine. Abou-Madi, Kieszler and Jacoub [2] showed that 1.5 mg kg^{-1} given i.v. before laryngoscopy was the optimal dose for attenuating this response. Using a similar anaesthetic technique, Tam, Chung and Cambell [3] observed complete attenuation of the response when this dose of lignocaine was given 3 min before laryngoscopy.

The aim of this study was to investigate this treatment under more standardized conditions, as previous studies were not comparable in design, patient selection criteria, monitoring or anaesthetic techniques.

PATIENTS AND METHODS

We studied 45 adult Chinese patients, with no history of hypertension or other cardiac disease. None was taking drugs with cardiovascular effects. All the patients were ASA I or II, and presented for elective thoracic surgery. Preoperative investigations included chest radiography, lung function tests and electrocardiogram.

The patients were premedicated with morphine 0.2 mg kg^{-1} and hyoscine 40 µg kg^{-1} i.m. 1 h before induction of anaesthesia. On arrival of the patient in the anaesthetic room and before induction of general anaesthesia, electrocardiographic monitoring was commenced and, after infiltration of the skin with 1 % lignocaine, a peripheral vein and radial artery were cannulated. The arterial cannula was connected to a Gould pressure transducer (calibrated immediately before and after each study period) and the signal was displayed on and recorded by a Honeywell OM monitor with integral hot wire recorder. Approximately 10 min elapsed between inserting the arterial cannula and induction of anaesthesia, to allow stabilization.

The patients were allocated to four groups using a random number table. Patients in group 1 (control) were given normal saline 4 ml i.v. over

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TABLE I. *Sex, age, weight and laryngoscopy to intubation time for each group (mean values (SEM)). Group 1 = Control; groups 2–4 = lignocaine 1.5 mg kg^{-1} i.v. over 30 s 3, 2 and 1 min, respectively, before laryngoscopy*

	Sex (F/M)	Age (yr)	Weight (kg)	Laryngoscopy to intubation times (s)
Group 1	4/6	44.7 (5.8)	50.5 (1.9)	12.2 (0.9)
Group 2	4/6	47.7 (3.9)	55.9 (1.8)	15.2 (1.8)
Group 3	3/7	45.5 (5.8)	56.7 (2.0)	16.8 (1.8)
Group 4	4/6	48.9 (3.8)	55.9 (3.6)	15.5 (1.6)

30 s, beginning 3 min before laryngoscopy. In groups 2, 3 and 4, patients were given lignocaine 1.5 mg kg^{-1} i.v. over 30 s, beginning 3, 2 and 1 min, respectively, before laryngoscopy.

Anaesthesia was induced with thiopentone 5 mg kg^{-1} given over 30 s, beginning 2.5 min before laryngoscopy. In a preliminary study, some of the patients moved during laryngoscopy; this was prevented during the main study by injecting a further bolus of thiopentone 1 mg kg^{-1} 1 min before laryngoscopy. Neuromuscular block was produced with a bolus of suxamethonium 1.5 mg kg^{-1} given 1.5 min before laryngoscopy.

At the same time as the initial injection of thiopentone was started, the patients began to breathe 65 % nitrous oxide in oxygen via a face mask and Mapleson A system. When the patient's breathing stopped, the anaesthetist manually ventilated the patient's lungs via the face mask using large tidal volumes and a slow ventilation frequency until tracheal intubation, after which the same pattern was continued via the tracheal tube. All laryngoscopies and subsequent tracheal intubations were performed by one of the two investigators, using a Macintosh laryngoscope and cuffed tracheal tube (Portex).

Arterial pressure was recorded from 30 s before the initial injection of thiopentone until 2.5 min after laryngoscopy. From the trace, heart rate (HR) and systolic (SAP) and diastolic (DAP) arterial pressures were measured and the mean arterial pressure (MAP) (diastolic pressure + 67 % pulse pressure) and rate–pressure product (RPP) were calculated. The time between laryngoscopy and intubation was noted, as was the ease of laryngoscopy.

Measurements were made at five times: pre-induction control reading (0 min); least arterial pressure between induction and laryngoscopy (2–3 min); immediately before laryngoscopy (3 min); greatest arterial pressure after laryngoscopy; end of the study period (5 min).

The data at each of the measurement points were compared using analysis of variance (ANOVA) for both absolute values and percentages of the controls. Other data were analysed using Student's paired t test. $P < 0.05$ was taken as significant.

RESULTS

Three patients were classed as having difficult tracheal intubations (> 30 s) and required repeat laryngoscopy or external displacement of the larynx. The recordings from a further two patients were of poor technical quality. The results from

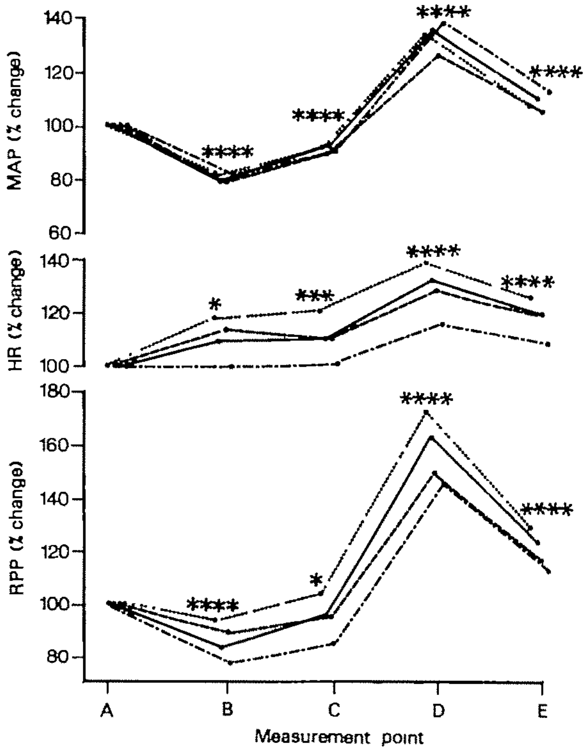

FIG. 1. Percentage changes in heart rate (HR), mean arterial pressure (MAP) and rate–pressure product (RPP) at each measurement point for each of the groups. A = Control reading; B = coinciding with lowest systolic arterial pressure; C = immediately before laryngoscopy; D = coinciding with the greatest systolic arterial pressure; E = end of the study period. ..... = Control (group 1); lignocaine 1.5 mg kg^{-1} i.v. over 30 s: —— = 3 min before laryngoscopy (group 2); —— = 2 min before laryngoscopy (group 3); –·– = 1 min before laryngoscopy (group 4). *$P < 0.05$; ***$P < 0.001$, ****$P < 0.0001$.

TABLE II. *Cardiovascular data (mean (SEM)). A = Control reading; B = coinciding with lowest systolic arterial pressure; C = immediately before laryngoscopy; D = coinciding with greatest systolic arterial pressure; E = end of study period. Group 1 = Control; groups 2–4 = lignocaine 1.5 mg kg^{-1} i.v. over 30 s, beginning 3, 2 and 1 min, respectively, before laryngoscopy*

	Group 1	Group 2	Group 3	Group 4
Heart rate (beat min^{-1})				
A	79 (6)	87 (5)	85 (6)	99 (5)
B	90 (5)	93 (3)	93 (5)	98 (5)
C	92 (3)	94 (3)	91 (4)	98 (4)
D	106 (4)	112 (3)	105 (4)	111 (4)
E	96 (5)	102 (3)	99 (5)	104 (4)
SAP (mm Hg)				
A	123 (5)	146 (7)	143 (8)	138 (5)
B	96 (4)	111 (6)	107 (5)	106 (3)
C	106 (5)	121 (4)	117 (6)	115 (4)
D	154 (7)	179 (8)	161 (11)	170 (6)
E	126 (8)	147 (7)	138 (12)	143 (5)
DAP (mm Hg)				
A	64 (3)	68 (2)	68 (3)	67 (3)
B	54 (3)	59 (2)	58 (3)	57 (2)
C	62 (3)	66 (2)	69 (3)	66 (3)
D	92 (4)	105 (3)	97 (6)	101 (4)
E	74 (4)	84 (2)	79 (5)	82 (3)
MAP (mm Hg)				
A	84 (4)	96 (3)	93 (4)	91 (4)
B	69 (3)	75 (3)	74 (3)	73 (2)
C	77 (4)	84 (2)	85 (3)	82 (3)
D	113 (5)	129 (4)	118 (7)	124 (5)
E	92 (5)	105 (3)	98 (7)	102 (3)
RPP (mm Hg beat min^{-1} × 10^3)				
A	9.8 (1.0)	11.7 (0.8)	11.6 (1.3)	13.6 (0.8)
B	8.8 (0.8)	9.7 (0.8)	9.3 (0.7)	10.4 (0.6)
C	9.8 (0.7)	10.8 (0.6)	10.5 (0.6)	11.3 (0.7)
D	16.4 (1.2)	18.7 (1.3)	16.3 (1.3)	19.2 (1.2)
E	12.2 (1.0)	14.3 (0 9)	12.9 (1.1)	15.0 (0.9)

these five patients have been excluded, leaving 10 patients in each group.

The four groups were similar with respect to age, sex, weight and time from laryngoscopy to tracheal intubation (table I).

There were no significant differences in cardiovascular variables between the groups (table II). The percentage changes in MAP, HR and RPP for each of the groups are shown in figure 1.

DISCUSSION

In this study, lignocaine 1.5 mg kg^{-1} given i.v. within 3 min of laryngoscopy failed to attenuate the cardiovascular responses to laryngoscopy and intubation. Laurito and co-authors [4] gave nebulized lignocaine 4 mg kg^{-1} over 15 min followed by i.v. lignocaine 2 mg kg^{-1} given 1 min before laryngoscopy, and Chraemmer-Jorgensen and co-authors [5] gave i.v. lignocaine 1.5 mg kg^{-1} beginning 2 min before laryngoscopy; both these studies showed that lignocaine had no significant effect on the cardiovascular effects of laryngoscopy and intubation compared with control groups. In contrast, Tam and co-workers [3], showed a beneficial effect only in a group given lignocaine 3 min before laryngoscopy. Abou-Madi and co-authors [2], using a similar interval between the injection of lignocaine and laryngoscopy, found only a "borderline statistical protection" against the response to laryngoscopy and intubation.

The cardiovascular changes produced by laryngoscopy are of a very rapid onset and short duration and should have been detected readily in the present study, using direct arterial pressure measurement, compared with previous studies using indirect measurement. Unfortunately, we were not able to measure end-expiratory carbon dioxide concentration ($P\mathrm{E}'_{\mathrm{CO_2}}$). We attempted to minimize changes in $P\mathrm{E}'_{\mathrm{CO_2}}$ by our choice of fresh gas flow and ventilatory pattern, and therefore presume that any change in $P\mathrm{E}'_{\mathrm{CO_2}}$ was of insufficient magnitude to alter autonomic activity significantly.

We attempted to produce similar degrees of pharyngo–laryngeal stimulation, by using a standard technique and excluding long and difficult laryngoscopies. Our results may, therefore, not be directly comparable with other studies which used different techniques. We excluded patients taking drugs acting on the cardiovascular system and patients with hypertension or ischaemic heart disease. Hypertensive patients, whether treated or not, show greater changes in arterial pressure than normotensive patients of the same age [6], and we cannot exclude a possible benefit of lignocaine in this group. We injected the lignocaine and thiopentone over 30 s in an attempt to produce similar peak plasma concentrations of drug in the different groups. Rapid i.v. injection of lignocaine may cause cardiovascular collapse in susceptible patients [7], and care should be taken.

There is some evidence that Chinese patients may have a slightly different pattern of cardiovascular response compared with similar non-Chinese patients [8]. This factor may have affected our results.

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DOSE-DEPENDENT EFFECT OF METOCLOPRAMIDE ON CHOLINESTERASES AND SUXAMETHONIUM METABOLISM

Y. J. KAO, J. TELLEZ AND D. R. TURNER

SUMMARY

In obstetric patients undergoing postpartum tubal ligation, we found that metoclopramide produced dose-dependent prolongation of suxamethonium-induced neuromuscular block. Mean block times after suxamethonium 1 mg kg^{-1} were 8.0 min, 9.83 min and 12.45 min for control and metoclopramide 10 mg and metoclopramide 20 mg groups, respectively. A laboratory study was therefore conducted on the inhibition of human plasma cholinesterase (PCHE) and erythrocyte acetylcholinesterase (ACHE) activity by varying concentrations of metoclopramide using acetylthiocholine as substrate. PCHE showed a greater sensitivity to inhibition by metoclopramide; the concentration of metoclopramide producing 50% inhibition of activity (I_{50}) was 3.16×10^{-7} mol litre^{-1}, which is within the therapeutic range. ACHE was less sensitive to inhibition by metoclopramide (I_{50} 2.24×10^{-5} mol litre^{-1}). Analysis of enzyme kinetics at varying substrate concentrations revealed that metoclopramide produced a potent non-competitive, dose-dependent inhibition of both ACHE and PCHE. The inhibition constant, Ki, was 1.88×10^{-7} mol litre^{-1} for PCHE and 9.5×10^{-8} mol litre^{-1} for ACHE. As metoclopramide is a potent inhibitor of PCHE, interactions might be expected to occur between metoclopramide and drugs that require PCHE for biotransformation, such as suxamethonium and ester local anaesthetics.

KEY WORDS

Complications: drug interactions. Enzymes: cholinesterases. Gastrointestinal tract: metoclopramide.

Metoclopramide is administered frequently before operation to decrease the incidence of perioperative nausea and vomiting, and to reduce the volume of gastric contents in patients considered at risk of aspiration pneumonitis. The latter group of patients usually also receives suxamethonium to facilitate tracheal intubation as part of a rapid sequence induction.

Analysis of the results of a clinical trial conducted at our Institution revealed that premedication with metoclopramide 10 mg i.v. led to significant prolongation of action of suxamethonium in a rapid sequence induction; no appreciable effect was observed when patients were premedicated with histamine type-2 antagonists (cimetidine, ranitidine and famotidine) 60–90 min before induction [1]. Data from the study on patients who received metoclopramide 20 mg were analysed and compared with those from the earlier study in order to determine the extent of the metoclopramide–suxamethonium interaction in clinical practice.

In vitro studies have concluded that metoclopramide produces a dose-dependent inhibitory effect on plasma cholinesterase (PCHE) activity in the dog and rabbit [2, 3] and erythrocyte acetylcholinesterase (ACHE) activity in the

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rabbit [3]. The interaction between metoclopramide and human ACHE and PCHE, however, has not been examined closely.

This study consisted of two parts: a clinical trial to determine the relationship between the dose of metoclopramide as preoperative medication and the degree of the prolongation of suxamethonium block, and a laboratory study designed to characterize the biochemical basis of the inhibitory effect of metoclopramide on human ACHE and PCHE activities.

SUBJECTS AND METHODS

Clinical study

We studied patients undergoing elective tubal ligation in the immediate postpartum period. Patients with a medical or family history of neuromuscular abnormality were excluded. Written informed consent was obtained from all patients and the study was approved by the Institutional Review Committee.

The design of the study has been reported previously [1]. Briefly, the patients were premedicated with lorazepam 1–2 mg by mouth 60–90 min before operation (control, $n = 21$). The patients in the remaining groups received lorazepam in addition to different doses of the study drugs i.v., 60–90 min before surgery. Anaesthesia was induced with thiopentone 4 mg kg^{-1} and sufentanil 50 μg, and maintained with 70% nitrous oxide in oxygen. Orotracheal intubation was facilitated by administration of suxamethonium 1 mg kg^{-1} i.v.

Neuromuscular block was measured with a Datex neuromuscular transmission monitor (NMT-Puritan Bennett, Inc.) which delivered a train-of-four (2-Hz) supramaximal stimuli every 10 s to a set of electrodes placed over the ulnar nerve. Sensing electrodes placed over the adductor pollicis muscle measured the resulting electromyographic activities. These signals were processed and plotted graphically as a percentage of control.

The time period from the onset of 95% depression of baseline electromyographic amplitude to 25% recovery was measured and designated as "duration of block". The anaesthetist who analysed the electromyogram was blinded to the premedication received by each patient. The data from all patients were analysed using the Newman–Keuls multiple range test. The data from the control and metoclopramide 10 mg and metoclopramide 20 mg groups are presented.

Laboratory study

A venous blood sample was obtained from a young, healthy volunteer. The PCHE activity was found to be 1660 u. $litre^{-1}$ and dibucaine number 86. The plasma and erythrocytes were separated by centrifugation and the erythrocytes washed three times with 100 volumes of sodium phosphate buffer 100 mmol $litre^{-1}$, pH 7.5. The plasma and packed erythrocytes were frozen at −70 °C until use. The 100-mmol $litre^{-1}$ phosphate buffer solution at pH 7.5, was used also as solvent to prepare the following reagents: 5,5′-dithio-bis (2-nitrobenzoic acid) (DTNB) 0.01 mol $litre^{-1}$; acetylthiocholine (ATCH) 0.001 mol $litre^{-1}$ (both reagents Sigma, St Louis, Missouri).

The activities of ACHE and PCHE were measured by the hydrolysis of the substrate ATCH as reported previously [4], but with the following modifications: 1-mmol $litre^{-1}$ ATCH 1 ml, 10-mmol $litre^{-1}$ DTNB 100 μl, metoclopramide in amounts ranging from 0 (control) to 1 mg, and enough phosphate buffer solution to make the final volume 3 ml; all incubated at 20 °C. Plasma 10 μl or lysed erythrocyte solution 150 μl was added. (The lysed erythrocyte solution was prepared by suspending 1 ml of the thawed erythrocytes in 100 ml of 10-mmol $litre^{-1}$ phosphate buffer, pH 7.5, followed by ultrasonic irradiation.) After equilibration for 1 min, the amount of product formed was calculated from the change in optical density at 412 nm using an LKB Biochrom model 4050 single-beam spectrophotometer. The rate of the increase of the optical density has been found to be linear over 10 min. Each assay was repeated three times and the mean values used for subsequent calculations.

The activities of ACHE and PCHE were determined also at 37 °C using the same method described above, and the results were compared with those obtained at 20 °C. As no significant difference was found, all subsequent assays were performed at 20 °C.

The metoclopramide inhibition constant, Ki, was calculated using a double reciprocal plot of the reaction velocity against varying substrate concentrations (Michaelis–Menten model of enzyme kinetics).

TABLE I. *Mean duration of neuromuscular block (min) after administration of suxamethonium 1 mg kg^{-1} to control and groups pretreated with metoclopramide (MCP) 10 mg and 20 mg i.v. *P < 0.05 compared with control group; P < 0.01 compared with both control and MCP 10 mg group*

Patient	Control	MCP 10 mg	MCP 20 mg
1	9.40	9.80	14.40
2	9.20	8.30	15.20
3	6.70	16.30	13.10
4	3.70	10.80	8.30
5	9.60	8.50	14.60
6	6.10	11.10	11.50
7	13.80	8.30	14.80
8	10.60	5.40	12.30
9	8.30	7.90	10.40
10	9.40	9.40	9.90
11	8.50	10.20	
12	7.10	12.30	
13	10.00	10.30	
14	9.80	9.40	
15	8.30	9.50	
16	8.10	13.40	
17	6.40	6.90	
18	5.20	9.00	
19	5.00	10.00	
20	7.50		
21	5.50		
Mean	8.00	9.83*	12.45**
SD	2.31	2.40	2.38

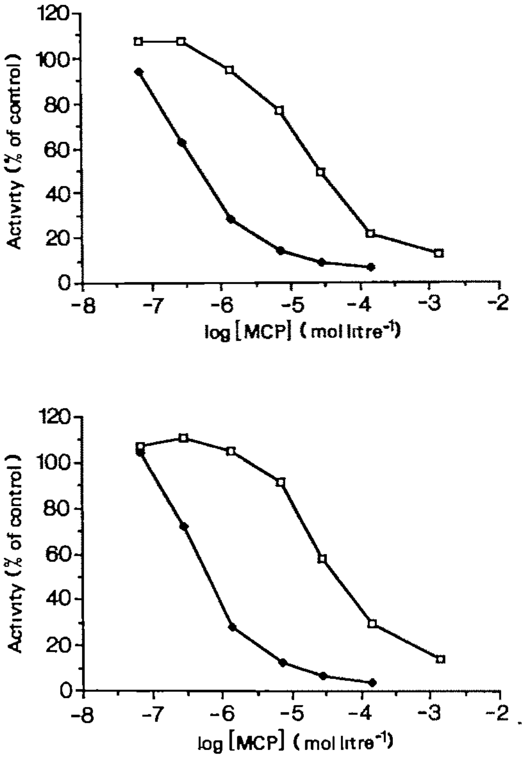

FIG. 1. Acetylcholinesterase (ACHE) (□) and pseudocholinesterase (PCHE) (◆) activity at different concentrations of metoclopramide (MCP) at 20 °C and 37 °C. The concentration of metoclopramide producing 50% inhibition of activity (MCP I_{50}) for both ACHE and PCHE can be determined from these plots.

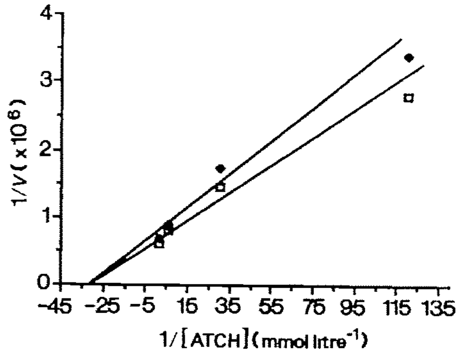

FIG. 2. ACHE enzyme kinetics. Double reciprocal plot of various concentrations of substrate (acetylthiocholine, ATCH), *vs* reaction velocity (*V*), in the presence of ACHE. Intersection of plots at *X*-axis indicates non-competitive nature of the inhibition of ACHE by metoclopramide. □ = Control; ◆ = metoclopramide 1.10 × 10^{-6} mol litre^{-1}.

RESULTS

Clinical study

The mean duration of neuromuscular block was 8.0 min in the control group, 9.83 min in group II (metoclopramide 10 mg i.v.) and 12.45 min in group III (metoclopramide 20 mg i.v.) (table I). The mean durations for groups II and III were significantly longer than control ($P < 0.05$ and $P < 0.01$, respectively), and significantly different ($P < 0.01$) from each other.

Laboratory study

Metoclopramide I_{50} values for ACHE at 20 °C and 37 °C were 2.24×10^{-6} mol litre^{-1} and 2.8×10^{-6} mol litre^{-1}, respectively, and the values for PCHE at 20 °C and 37 °C were 3.16×10^{-7} mol litre^{-1} and 4.17×10^{-7} mol litre^{-1}, respectively (fig. 1).

The inhibition constants (*K*i) at 20 °C were 9.53×10^{-8} mol litre^{-1} and 1.88×10^{-7} mol litre^{-1} for ACHE and PCHE, respectively (figs 2, 3). The inhibition of ACHE and PCHE by metoclopramide was dose-dependent and non-competitive in nature. *V*max values for ACHE and

PCHE were 1.43×10^{-5} mol litre^{-1} min^{-1} and 5.32×10^{-6} mol litre^{-1} min^{-1}, respectively. The Michaelis constant (*K*m) was 2.63×10^{-2} mol litre^{-1} for ACHE and 4.55×10^{-2} mol litre^{-1} for PCHE.

DISCUSSION

The plasma concentration of pseudocholinesterase changes during pregnancy. Immediately postpartum, the enzyme concentration remains reduced for 2–7 days. Therefore, compared with a normal population, suxamethonium sensitivity may be more likely to present in obstetric patients.

Metoclopramide (methoxychloroprocainamide) is a benzamide derivative, structurally similar to procainamide, with a wide range of pharmacological effects. Antagonism at dopamine type-2 receptors produces extrapyramidal symptoms and release of prolactin. Similarly, via interaction with the chemoreceptor trigger zone, metoclopramide produces centrally-mediated antiemetic effects. It is also a cholinomimetic agent which produces gastrointestinal motility changes such as increased oesophageal contractions, increased lower oesophageal sphincter pressure and an increase in anterograde peristalsis. *In vitro* studies have demonstrated that the drug potentiates the contractions of gastrointestinal smooth muscle produced by acetylcholine, but that it has no such effect in the absence of acetylcholine [5]. This finding is consistent with the clinical observation that metoclopramide produces a more significant change in peristalsis in normal patients than in patients who already have reduced peristaltic activity or autonomic neuropathy. Therapeutic blood concentrations [6] of metoclopramide inhibit PCHE, suggesting that the mechanism of its effect on gastrointestinal motility may be partly via potentiation of acetylcholine activity by inhibition of PCHE. This would suggest that the cholinesterase present in the parasympathetic ganglia of the gastrointestinal tract is of the PCHE type. PCHE and ACHE inhibition are probable contributing factors in the bronchospasm reported after administration of metoclopramide [7].

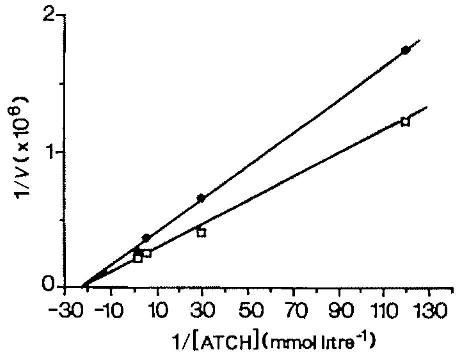

FIG. 3. PCHE enzyme kinetics Double reciprocal plot of various concentrations of substrate (acetylthiocholine, ATCH), *vs* reaction velocity (*V*), in the presence of PCHE Intersection of plots at *X*-axis indicates non-competitive nature of the inhibition of PCHE by metoclopramide. □ = Control; ◆ = metoclopramide 8.89×10^{-8} mol litre^{-1}.

The fact that metoclopramide is a potent inhibitor of PCHE raises the possibility of adverse drug interactions when drugs that depend on PCHE activity for biotransformation are given to patients who have been pretreated with metoclopramide. In the case of ester-type local anaesthetics, administration of metoclopramide might be expected to slow metabolism and increase the risk of toxic reactions such as central nervous system toxicity and cardiovascular depression. In the case of suxamethonium, it could prolong neuromuscular block.

In a study of concentrations of the pseudocholinesterase enzyme and the duration of suxamethonium-induced neuromuscular block, Viby-Mogensen discovered that the duration of block remained relatively constant over a wide range of enzyme activity. Thus, in a normal population, the plasma concentration of cholinesterase cannot be used to predict the duration of the suxamethonium-induced neuromuscular block. Furthermore, it has been shown that prolongation of such a block does not occur until only 50% of PCHE activity remains (from our study, this would require a metoclopramide concentration of 3.16×10^{-7} mol litre^{-1}). Furthermore, the prolongation of suxamethonium block increases exponentially with further inhibition of PCHE activity [8]. Pharmacokinetic studies of metoclopramide suggest that the blood concentration 1 h after administration of 10 mg i.v. is approximately 1.5×10^{-7} mol litre^{-1} [6]. Blood concentrations following a dose of 20 mg i.v. should inevitably be greater and may exceed the critical concentration for 50% inhibition of PCHE.

In our clinical study, metoclopramide prolonged the duration of block induced by suxamethonium 1 mg kg^{-1} in the puerperal patient in a dose-dependent manner by 23% and 56% compared with controls after a dose of 10 or 20 mg, respectively, was administered i.v. 60 min before induction. The prolongation of suxamethonium block after metoclopramide 20 mg i.v. is more than twice that produced by metoclopramide 10 mg i.v. These findings are consistent with the exponential nature of the suxamethonium block and PCHE activity relationship [8].

We conclude that obstetric patients receiving metoclopramide and suxamethonium should be monitored closely.

ACKNOWLEDGEMENT

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EXTRADURAL, SPINAL OR COMBINED BLOCK FOR OBSTETRIC SURGICAL ANAESTHESIA

L. E. S. CARRIE

One of the outstanding features of obstetric surgical procedures carried out under regional anaesthesia is that the patients are seldom given premedication, peroperative sedation or light general anaesthesia which might mask any deficiencies in the local anaesthetic block. Before delivery this is in the interests of the fetus, which may be affected by any drugs given to the mother. For procedures carried out after delivery, sedation or anaesthesia interferes with the mother's enjoyment of her new baby, and may even jeopardize her safety if her respiratory protective reflexes are depressed. This is in contrast with other branches of anaesthesia in which regional techniques are popular—especially orthopaedics, where supplementary sedation or anaesthesia is commonplace. It is in obstetric anaesthesia, therefore, that the differences between extradural and spinal block may be most apparent, and in choosing between them it is necessary that the anaesthetist understands the relative merits of the two techniques.

In accordance with popular usage, "anaesthesia" is used in this article, rather than "analgesia", although much of the time only freedom from pain is implied. In addition, "subarachnoid" and "intrathecal" are used synonymously with "spinal".

FACTORS AFFECTING THE CHOICE BETWEEN EXTRADURAL AND SPINAL ANAESTHESIA

General factors affecting the choice between extradural and spinal anaesthesia always include the expertise of the anaesthetist and the availability of suitable drugs and equipment. Historically, spinal anaesthesia antedated extradural anaesthesia by a few years, but its popularity in the United Kingdom was dealt a severe blow in the 1950s by the publicity surrounding the *Woolley and Roe* case [15], when two patients on one operating list became paraplegic. Only recently has this type of regional block returned to favour. In the meantime, much expertise in its use was lost, as indicated by the recent "discovery" that inserting the spinal needle through the dura mater with its bevel orientated laterally reduces the incidence of spinal headache [52], although this had been recommended more than 40 years previously [26, 48].

In the United Kingdom, the combination of the strict requirements of the Committee on Safety of Medicines (CSM), the low usage of spinal anaesthesia for many years after the *Woolley and Roe* case and a virtual monopoly of the local anaesthetic market by one drug company, has led to a very restricted choice of agents. Only one hyperbaric spinal solution—heavy bupivacaine—has a product licence in the United Kingdom, and only the various formulations of bupivacaine are available in packaging suitable for extradural block. Two per cent lignocaine with adrenaline, currently popular for operative obstetrics, must be prepared by adding adrenaline to the plain solution, a technique which has some advantages but also has potential for contamination or errors in dilution. In some other countries, the choice of local anaesthetic agents for extradural and spinal block is so wide as to be almost confusing, but it does give the individual anaesthetist greater flexibility in choosing the agent for a particular purpose.

Several other factors affect the choice between extradural and spinal block.

KEY WORDS

Anaesthesia, obstetric Anaesthetic techniques· extradural, spinal.

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Speed of Onset

The time required to prepare a patient for surgery using a regional technique consists of two parts: the time taken in performing the technique and the time from injection of the drug to the onset of surgical anaesthesia. Because the technique is simpler, it should require less time to perform a spinal than an extradural block, especially if a catheter is introduced in the latter. After injection intrathecally, drugs usually have more rapid onset of effect than after extradural injection, although there is some variation in rate of onset between individual drugs injected by both routes. Chloroprocaine (not available in the United Kingdom) is an exception, in that extradural administration may result in almost as rapid an onset of effect as is obtained with other drugs given intrathecally.

The difference in rate of onset of surgical anaesthesia also varies with different operation sites. For example, perineal anaesthesia is relatively slow in onset after extradural block, because of the distance of the sacral roots from the site of injection, whilst after spinal block it occurs almost immediately.

Various modifications may be made to extradural anaesthesia in order to hasten its onset.

Alkalinization (pH adjustment)

Local anaesthetics are weak bases and poorly soluble in water. They are usually supplied commercially as the hydrochloride salts with a relatively low pH to keep the base in solution. Adrenaline-containing solutions are particularly acidic. In solution, such weak bases exist in two forms: cationic and non-ionized free base. It has been shown that, while the cationic form interacts with the axonal membrane to block nerve conduction, only the lipid-soluble free base penetrates the nerve sheath [67–69]. The proportion of the latter may be increased by increasing the pH of the solution; clinically this is achieved by adding bicarbonate to the local anaesthetic solution. The amount required varies between agents [35], but the value to which the pH may be increased is limited by precipitation of the free base at about pH 7.

Significant reductions in onset time have been claimed for extradural mepivacaine [28], lignocaine [22], bupivacaine [24] and chloroprocaine [64, 75]. All investigators do not agree with these findings, however, especially with respect to bupivacaine [76]. It is difficult to reconcile such differences, but they may be explained at least partly by use of different end-points (e.g. onset time, onset of surgical anaesthesia, time to peak effect) or different methods of measuring levels of analgesia (e.g. pinprick, electrical stimulation, loss of temperature sense). Further clarification is required, but while the results with lignocaine appear convincing, those with bupivacaine were statistically significant, rather than clinically dramatic, in the series reported by Douglas and colleagues [24], in which the average time to peak effect was reduced from 25 to 18 min.

Carbonation

Bromage and colleagues [6] showed that carbonation decreased the latency of onset of lignocaine (by about 33%) and prilocaine (by about 25%). Not all subsequent studies have confirmed these results [49, 53]. Carbonation may produce this effect in several ways: carbon dioxide itself may cause some direct neural block, increased concentrations of carbon dioxide may result in an increase in the cationic form of the local anaesthetic within the axoplasm, and there may be an increase in the pH of the solution as carbon dioxide is lost on opening the ampoule. Brown and colleagues showed that carbonation had little effect on the speed of onset of anaesthesia with bupivacaine [7].

Warming

Mehta and colleagues [50] and Howie and Dutton [32] showed that warming 0.5% bupivacaine to approximately 38.0 °C produced a reduction in onset time. The improvement (of about 20%) hardly merits the inconvenience of the recommended warming of both the extradural solution and tray.

Efficacy

Apart from safety, efficacy is the most important aspect of a local anaesthetic block especially if, as in obstetrics, i.v. or inhalation supplementation is undesirable. After extradural injection, local anaesthetic solution must percolate through fat and veins to reach the nerve roots; as many as 38 pairs may require blocking to provide surgical anaesthesia up to the 4th thoracic dermatome. It is perhaps surprising that extradural blocks work as well as they do. However, in awake patients, extradural block may sometimes be patchy, asymmetrical or limited in extent, and may remain so despite increments of local anaesthetic drug. In recent years, evidence has accumulated to explain these findings. Based on surgical and postmortem dissections and radiography of the extradural space, Luyendijk [45–47] described a median dorsal fold of the dura mater with variable attachment to the vertebral arches and ligamentum flavum. Clearly, this fold could direct local anaesthetic solution wholly or partly to one side of the extradural space. Using polyester resin injection studies of the extradural space, Husemeyer and White [34] confirmed the presence of this midline dorsal fold, with a tendency for the resin to become compartmentalized rather than distributed symmetrically. The presence of variable midline bands and structures in the posterior extradural space was reported also by Blomberg [4] using extraduroscopy and by Savolaine and colleagues, using computed tomography scanning [72].

In the cerebrospinal fluid of the subarachnoid space, local anaesthetic solutions behave usually as if totally unimpeded by physical barriers. Sometimes there may be difficulty in extending or limiting a spinal block, but patchiness is most unusual. Indeed, efficacy is one of the main advantages of this technique. Subarachnoid septa do exist [55], especially in the midline posteriorly and postero–laterally, but they are incomplete and a unilateral subarachnoid block as described by Armstrong [3] is exceptional.

Assessment of efficacy of regional anaesthesia for Caesarean section is made usually either by a simple scoring system or by noting the proportion of patients requiring i.v. or inhalation supplementation. Using these criteria, Norton, Davis and Spicer [56] compared 0.5% bupivacaine plain with 2% lignocaine with adrenaline 1:200000 and found that only 50% of patients were completely comfortable in both groups. Reid and Thorburn [65], comparing the same drugs, had similar success with bupivacaine, but only 29% of those given lignocaine required supplementation. Tackley and Coe [77] also found that 50% of patients required peroperative supplementation after extradural block with 0.5% bupivacaine plain for elective Caesarean section, but none of a small number given pH-adjusted 0.5% bupivacaine with adrenaline 1:200000 required supplementation. Similarly, Scott and colleagues [74] achieved adequate analgesia for lower abdominal surgery in only 60% of patients when using 0.5% bupivacaine, although the success rate was increased to 90% by use of 0.75% bupivacaine. It seems that, in some subjects, the anatomical structures mentioned above may prevent the 0.5% bupivacaine from reaching the nerve roots in adequate concentration but, when 0.75% bupivacaine is used, the small amount reaching the nerve roots may still be sufficient to produce effective analgesia. Although some of the drugs in the studies noted above were given in divided doses, it is likely that a slow incremental technique with repeated "painting" of the nerve roots may be more successful in producing satisfactory anaesthesia. This technique, which may be very time consuming, was recommended by Crawford [18] without any maximum limit being put on the dose of drug.

Extradural opioids

Since the discovery of opioid receptors in the brain and spinal cord and of endogenous opioids, the use of extradural opioids has been evaluated in several painful conditions. In acceptable doses, alone, they do not provide adequate pain relief in labour, but they have become popular, especially in the United States, in combination with local anaesthetic solutions for this purpose. More recently there has been growing enthusiasm for the addition of opioids to local anaesthetic solutions in order to improve the efficacy of pain relief during extradural anaesthesia for Caesarean section. A survey of members of the Society for Obstetric Anesthesia and Perinatology in 1987 [39] showed that 62% were adding an opioid to local anaesthetic drugs—perhaps indicating dissatisfaction with unmodified local anaesthetic block. The commonest supplementary agent was fentanyl, given in a dose of 100 µg after delivery of the baby. The percentage of American obstetric anaesthetists now using opioids in this way is probably much greater. The reports by Preston and colleagues [59], who added fentanyl to 2% lignocaine with adrenaline and Gaffud and colleagues [27] who added the same drug to 0.5% bupivacaine with adrenaline, are typical of several studies of this technique. It is interesting to note that, while both groups reported an improvement in efficacy of extradural anaesthesia, complete pain relief was not produced in all patients.

Addition of adrenaline

The main reason for addition of adrenaline to local anaesthetic solutions is to delay absorption from the site of injection, thus increasing the duration of action and reducing systemic toxicity.

This effect is marked with lignocaine, but is less (if at all) evident with bupivacaine. It is debatable if adrenaline increases the intensity of the block but, if so, it may produce this effect by direct action on alpha-adrenergic receptors (which mediate analgesia) in the spinal cord. Laishley and Morgan [41] compared 0.5% bupivacaine plain and with adrenaline 1:200000 for elective Caesarean section and observed a significant reduction (from 45% in the former group to 25% in the latter) in the number of those requiring any form of extradural, inhalation or i.v. supplementation after an initial 100-mg dose.

Other agents

Several other supplementary agents have been evaluated, including clonidine (an alpha-2-adrenergic stimulator) [44], somatostatin (a tetradecapeptide) [13] and ketamine [58]. Results have been inconsistent and, in common with opioids, these agents seem to be more effective against some types of pain than others. None has been shown to improve surgical anaesthesia reliably.

Efficacy of Spinal Anaesthesia

Because of the ease of access of local anaesthetic solutions to the nerve roots in the subarachnoid space, a high success rate depends mainly on the use of an effective drug and a technique which ensures that it reaches the nerve roots in sufficient concentration to last for the duration of the operation. This is relatively difficult to achieve for Caesarean section, for which the block must be maintained in the upper abdominal segments where "painting" of the nerve roots by the local anaesthetic agent is least effective. Thus Abouleish and colleagues [1] and Santos and colleagues [71], using up to a maximum of 10 mg of hyperbaric 0.5% bupivacaine found that many patients required peroperative i.v. supplementation. On the other hand, Michie and his colleagues [51] reported no need for supplementation in 20 patients in whom 12.5 mg (2.5 ml of 0.5% hyperbaric solution) was used—a result consistent with my own experience using a fixed dose of 14 mg (2.8 ml of 0.5% solution) in almost all patients [unpublished observations].

Because of unpredictable spread in obstetric patients, plain solutions of local anaesthetics, which are approximately isobaric, are not recommended for Caesarean section—even in expert hands [70]. However, Van Zundert and colleagues [80] reported excellent analgesia with a low incidence of hypotension when a large volume (10 ml) of 0.125% bupivacaine with 1:800000 adrenaline was used. However, some blocks did reach the mid-cervical nerve roots.

Toxicity

In terms of drug toxicity, spinal anaesthesia is outstandingly the safest of all regional and general anaesthetic techniques. However, all local anaesthetic agents are toxic in large doses and in the case of extradural anaesthesia the safe limits must always be respected. This applies especially when an extradural block which has been established for pain relief in labour is extended for Caesarean section. In these circumstances, toxic plasma concentrations may be produced [78] and convulsions have been reported [79]. Cardiac arrest caused by bupivacaine has been reported in the U.S.A. [2]; while this was reported to have occurred after intravascular injection, the danger is sufficient to make most anaesthetists reluctant to use large doses of this agent. It should be noted that the U.K. data sheet for bupivacaine no longer recommends the use of 0.75% bupivacaine in obstetric indications and the United States Food and Drug Administration has also withdrawn approval for its use in obstetrics.

Headache

Headache does not usually follow a correctly performed extradural block, but may result if the dura is punctured accidentally and is likely to continue for as long as cerebrospinal fluid leaks into the extradural space. The postural nature of this headache, its frequent association with neck ache and less often with photophobia, vertigo, tinnitus or even cranial nerve palsies is well known. It is also known to be (but not why it is) commonest in women of childbearing age, generally commoner in women, less common in the very old and almost unknown in the very young. The incidence and severity are related to the size of the needle puncturing the dura mater, so that the greatest incidence (approximately 70%) is seen when inadvertent dural puncture occurs with a large extradural needle in pregnant patients [17].

In the past, the susceptibility of obstetric patients to headache even after the use of relatively fine needles has deterred anaesthetists from using spinal anaesthesia, but recent improvements in needle manufacture have made available a wide range of excellent, sharp disposable needles in sizes as small as 26 gauge. It is claimed that the incidence of headache is reduced by needle insertion with the bevel parallel to the longitudinal fibres of the dura [52], although it has been disputed that such an arrangement of the dural fibres exists [23]. Even with 26-gauge needles inserted in this manner, several studies have reported a significant incidence of postural headache of 3–8%, which is consistent with an incidence of 3% in more than 1500 spinal blocks for several obstetric indications [unpublished observations]. Not all these headaches are severe, but an extradural blood patch is required occasionally and these few cases suggest that even finer needles should be used. Flaatten and colleagues [25] reported no postural headaches in 42 young patients (11 female) after the use of 29-gauge needles, and in a personal series (to date) of 130 anaesthetics for Caesarean section carried out using 29-gauge needles in a combined spinal–extradural technique there have been no reports of postural headache.

Hypotension

Extradural or spinal block only causes hypotension if the sympathetic outflow from the spinal cord is affected. Thus sacral block alone has no effect on arterial pressure, mid block to the lower thoracic dermatomes may have some effect and high block to the upper thoracic levels produces extensive sympathetic block, likely to cause hypotension. With extradural and spinal blocks of equal extent, a similar effect on arterial pressure might be expected. In practice, however, spinal blocks have a greater tendency to cause hypotension because the speed of onset of intrathecal block exceeds the rate at which compensatory physiological responses develop. Indeed Parnass, Curran and Becker [57] attributed the greater degree of hypotension when bicarbonate was added to lignocaine with adrenaline for extradural Caesarean section to the greater speed of onset of the pH-adjusted drug.

Other factors affect the degree of hypotension, including the state of hydration, blood loss, pre-existing cardiovascular disease and concomitant antihypertensive therapy. Regional anaesthesia to the upper thoracic dermatomes may produce bradycardia resulting from block of cardio-accelerator nerves although, in obstetric patients, severe bradycardia is unusual even with high blocks. In the latter weeks of pregnancy, the most important factor affecting arterial pressure is aorto–caval occlusion, which potentiates the sympathetic block.

The most important prophylactic measures against hypotension during the extensive sympathetic block inevitably caused by regional anaesthesia for Caesarean section are fluid preloading and maternal posturing to minimize aorto–caval occlusion. The full lateral posture should be maintained whenever possible [10]. It is debatable if crystalloids or colloids should be used for preloading, but most anaesthetists prefer the former; doubt has been expressed on whether or not colloids are more effective [61] and all are associated with anaphylactoid reactions, especially in unstressed patients. A vasopressor may be required, and for this purpose the predominantly beta-adrenergic stimulator ephedrine, which does not reduce placental blood flow [60], is the most popular agent. It has been given by various routes and doses, but the most flexible method during spinal anaesthesia for Caesarean section is a prophylactic i.v. infusion at a rate of administration titrated against arterial pressure [38]. During extradural Caesarean section, most anaesthetists would only give ephedrine if required. Another approach is to promote venous return by the use of elastic support stockings [30]. While this seems a rational measure, not all are convinced of its efficacy [42].

Hypotension in obstetric patients is variously defined as a reduction in systolic arterial pressure to a value less than 90 or 100 mm Hg, or a reduction in systolic arterial pressure by 20–30% of its preanaesthetic value. Using these definitions, it has been shown, using Apgar scores [5], fetal blood-gas tensions [19], intervillous blood flow measurements [36], ultrasound measurement of the fetal circulation [43] and neurobehavioural adaptation scores [16], that transient hypotension does not adversely affect the fetus.

Effect on Respiration

Before the significance of aorto–caval occlusion in pregnant patients was appreciated, cardiovascular collapse occurring during Caesarean section under spinal anaesthesia was attributed frequently to respiratory depression. It was assumed that this was caused by a combination of intercostal muscle paralysis from the high block and restriction of descent of the diaphragm by the gravid uterus. These incidents are now known to have been caused by aorto–caval occlusion. It appears that respiration is well maintained, even when spinal anaesthesia affects the highest thoracic segments. It is likely that this is caused partly by the continued ability of the near-term pregnant woman to perform diaphragmatic breathing, and partly by the differential nature of both extradural and spinal blocks in their higher segments, motor function being less affected.

Using reduction in peak expiratory flow rate (PEFR) as a measure of ability to cough, Gamil [29] found that the majority of women during extradural Caesarean section maintained PEFR at values consistent with effective coughing. However, women with pre-existing respiratory disease may have impaired ability to cough in these circumstances, and Gamil recommended the avoidance of sedative supplementation. She also suggested that postoperative patients should not be nursed in the flat supine position until regression of the extradural block was complete.

Continuous Technique

One of the most frequently stated disadvantages of spinal compared with extradural block is that it is unwise to place a catheter in the subarachnoid space—that is, it is a non-continuous technique. Two reasons are offered, neither of which has been substantiated. The first is that infection is more likely to result than with an extradural catheter and the second is that a prohibitive incidence of post-spinal headache would result from the large size of the needle required to introduce the catheter.

Several series [21, 31, 37] of continuous spinal blocks have been reported with no evidence of infection, and it seems that the risk of infection has been exaggerated, at least when catheters are left in place for only a few hours.

In 1972, Kallos and Smith [37] reported a continuous spinal technique using 20-gauge catheters inserted through 18-gauge needles without any subsequent postural headaches. This surprising observation was supported more recently by Denny and colleagues [21], who reported only one postural headache in 117 patients using the same sizes of needle and catheter. The explanation for this remarkably low incidence of headache was suggested from the observation of Yaksh and colleagues [81] that, in cats with indwelling intrathecal catheters, an inflammatory response with fibrin deposition occurred round the needle hole in the dura mater. The mean age of patients in Denny's series was 63 yr, with more men than women, while Kallos and Smith's group, with a similar composition, were immobilized supine for 5 days (for surgical reasons). On the other hand, Giuffrida and colleagues [31] found an unacceptably high incidence (16 %) of postural headache in 74 obstetric patients in whom continuous spinal catheters had been introduced through 21-gauge needles.

Another new development is the introduction of 32-gauge microcatheters which may be passed through some types of 26-gauge spinal needle [33]. If these catheters prove safe and reliable, they may permit continuous spinal techniques; for example, continuous spinal anaesthesia might be used during surgery to maintain a high intensity of anaesthesia, followed by more dilute concentrations of local anaesthetics (or even opioids) for postoperative pain relief. It is important that such techniques are considered only when the available facilities are adequate for their safe use.

COMBINED SPINAL–EXTRADURAL TECHNIQUES

As both extradural and spinal blocks have advantages, there should be some benefit in combining the two techniques, provided there is no increase in the incidence of complications. The combined technique, whereby a long spinal needle is introduced through an extradural needle, was first described for orthopaedic use by Coates [14] and by Mumtaz, Daz and Kuz [54]. Its use in obstetrics was reported first in 1984 [12], although Brownridge in 1981 [8] had described the technique using separate interspaces. Since then, several reports have appeared [9, 11, 20, 40, 62] and the combined technique has gained sufficiently in popularity for one equipment company (Braun Medical Ltd) to have produced packs with several matching sizes of extradural and spinal needles. Usually, 25- or 26-gauge spinal needles are used, but trials have been carried out with even finer needles (see above). This combination of techniques provides the rapid onset and reliability of spinal block with the facility to modify the analgesia (by supplementation through the extradural catheter) if it is not effective. In the postoperative period, local anaesthetic, opioids, or both, may be administered by incremental or continuous techniques. A further advantage of this technique is that, during insertion, the extradural needle guides the fine spinal needle almost to the subarachnoid space.

With the combined technique, greater flexibility is available in providing regional anaesthesia. For example, spinal block may be used alone for the surgical procedure or combined with extradural anaesthesia from the outset. Another variation advocated for Caesarean section [63] is the limitation of the spinal anaesthetic to the lower segments and extension with the extradural. Other possibilities, where proper facilities are available, are to give an intrathecal injection of an opioid in labour, adding extradural analgesia if and when required [Gutsche, personal communication], or to use intrathecal opioids combined with local anaesthetic agents for both peroperative and postoperative pain relief [1].

CONCLUSION

Several factors must be taken into account in choosing between extradural and spinal anaesthesia for surgery. Spinal block, especially in the sacral segments, provides more rapid onset of surgical anaesthesia than extradural block, although the rather short-acting chloroprocaine, not available in the U.K., may be almost as rapid when given by the extradural route.

Because spinal local anaesthetic solutions are injected into the cerebrospinal fluid directly bathing the nerve roots on which they are to act, they usually produce effective anaesthesia; extradural solutions must overcome variable anatomical barriers. The more potent and concentrated the local anaesthetic drug, the more likely it is to be effective despite anatomical barriers. Bupivacaine 0.75% approached this ideal, but fears of toxicity led to withdrawal of its approval for use in obstetrics. While discussing extradural block for surgery, Scott [73] stated "The evidence that it is not possible with current local anaesthetic drugs to produce 100% analgesia in 100% of patients is not hard to find" and anaesthetists still await a drug with outstanding extradural efficacy. A new agent—ropivacaine—is currently undergoing clinical trials.

Because of the very small doses used for spinal anaesthesia, drug toxicity is most unlikely. With extradural anaesthesia, drug toxicity is more likely to be encountered, especially when large volumes of local anaesthetic are used in an attempt to overcome a recalcitrant block. If an agent is to be injected over a period of time, the maximum safe dose may be uncertain. In the case of bupivacaine, however, an attempt has been made to give some guidelines [66]. Toxic convulsions have been described when extending an extradural already in use for labour for Caesarean section [79], and when such blocks are difficult to extend it is safer to replace the extradural catheter or even to add a spinal block.

The rapid onset of spinal anaesthesia makes hypotension more likely when block involves the sympathetic outflow from the spinal cord. This implies that particular vigilance is required during spinal anaesthesia for Caesarean section, where aorto–caval compression increases the likelihood of hypotension.

Surprisingly few general surgical patients complain of headache following the introduction of intrathecal catheters through quite large needles. However, we might expect a higher incidence in pregnant women, limiting the usefulness of such devices in obstetrics. While microcatheters may resolve this difficulty, their practicality has yet to be demonstrated.

Finally, combined spinal–extradural techniques provide the speed and reliability of spinal anaesthesia with the advantages of a continuous catheter technique and greater flexibility in providing high quality analgesia, both during and after surgery.

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SPINAL ANAESTHESIA WITH HYPOBARIC 0.19% OR PLAIN 0.5% BUPIVACAINE

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SUMMARY

Hypobaric 0.19% bupivacaine (plain 0.5% bupivacaine 3 ml + distilled water 5 ml) was compared with 0.5% plain bupivacaine 3 ml for spinal anaesthesia in 29 healthy patients undergoing orthopaedic surgery of the lower extremities. The solutions were injected at the L3–4 interspace in 40 s, and patients were kept sitting for 2 min after injection. The mean maximal cephalad spread of sensory block was to the T1 segment (SD 3.6) and to T8 (4.1) in the hypobaric and plain bupivacaine groups, respectively ($P < 0.0001$). The study was interrupted after observing the sensory block of the 29th patient (hypobaric bupivacaine) spread to C2 within 5 min of injection. In most patients, the hypobaric bupivacaine block affected the upper thoracic nerves, and in three patients the cervical nerves also. The high levels of block were accompanied by marked hypotension. The extensive spread of the blocks makes this hypobaric spinal anaesthesia technique unsuitable for routine use.

KEY WORDS

Anaesthetics local: bupivacaine. Anaesthetic techniques spinal.

Plain 0.5% bupivacaine acts as a slightly hypobaric solution when used for spinal anaesthesia [1, 2]. Keeping the patient sitting for 2 min after injection of the anaesthetic results in a higher spread of the block than in patients kept supine immediately after injection [3]. Stienstra and co-workers [4] made the plain bupivacaine solution more hypobaric by heating it to 37 °C and injecting it into the subarachnoid space of patients who were kept sitting for 3 min after injection. This resulted in a relatively extensive cephalad spread of analgesia with low variability.

The baricity of plain bupivacaine solution can be decreased by adding known quantities of water. It is not known if the subarachnoid injection of a hypobaric solution prepared in this manner would result in a more cephalad and less variable spread of the spinal block than that achieved with the commonly used plain 0.5% bupivacaine. The present study was designed to examine this question.

METHODS AND RESULTS

We studied 29 ASA I patients, aged 20–58 yr, undergoing orthopaedic surgery of the lower extremities under spinal anaesthesia. Local Ethics Committee approval and informed consent from the patients were obtained. Our intention, initially, was to study 40 patients in two comparable groups, but because of the development of dangerously high blocks, the study was discontinued. Premedication comprised diazepam 0.15 mg kg^{-1} by mouth. Lactated Ringer's solution 1.5 ml kg^{-1} i.v. was administered before injection of the anaesthetic and 6 ml kg^{-1} during 30 min thereafter. During surgery the infusion rate was approximately 50 ml h^{-1}.

Spinal anaesthesia was performed using a 25-gauge needle at the L3–4 interspace, with the patient in the sitting position, in which they remained for a further 2 min. In a random order, 14 patients (11 male) received plain 0.5% bupivacaine 3 ml diluted with distilled water up to 8 ml—that is, 0.19% bupivacaine (measured density 0.9974 g ml^{-1} at 21 °C) and 15 patients (eight male) received plain 0.5% bupivacaine 3 ml (density 1.004 g ml^{-1} at 21 °C) over 40 s. The

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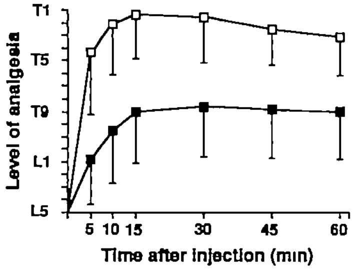

FIG. 1. Mean (SD) onset of analgesia following intrathecal injection of hypobaric 0.19% bupivacaine 8 ml (□) or plain 0.5% bupivacaine 3 ml (■). Bars indicating standard deviations have been plotted in only one direction for clarity.

spread of analgesia was studied by pinprick (27-gauge needle) and motor block was assessed using a modified Bromage scale (0–3) by a blinded observer. Decreases in mean arterial pressure (MAP) of more than 25% of control were treated with ephedrine 0.07 mg kg^{-1} i.v. Bradycardia (heart rate less than 45 beat min^{-1}) was treated with atropine 0.008 mg kg^{-1} i.v.

Statistical analyses were performed, as appropriate, using Mann–Whitney *U* test, Student's *t* test, regression analysis and chi-square test.

The study groups were comparable in age, weight, height, body mass index, baseline MAP and heart rate.

A mean maximal cephalad spread of analgesia to the T1 (SD 3.6) and T8 (4.1) segment was observed in the hypobaric bupivacaine and plain bupivacaine groups, respectively ($P < 0.0001$). The mean maximal extension of analgesia was reached in 11.4 min in the hypobaric group and in 24.0 min in the plain group ($P < 0.005$). The spread of analgesia remained significantly higher in the hypobaric group than in the plain group at each time of testing between 5 and 60 min (fig. 1) ($P < 0.0005$).

After the 29th patient, whose sensory block spread to the C2 level, the study was discontinued. This patient reported that he could not breathe normally, and he had paraesthesiae in the upper extremities. Five minutes after injection of the anaesthetic, MAP had decreased by 25% (to 71 mm Hg at the lowest), and one dose of ephedrine was given. The patient received oxygen by nasal catheter; the pulse oximeter showed 98% saturation throughout the anaesthesia. In another two patients in the hypobaric group, pinprick analgesia spread to the cervical segments (C2, C6). The time from injection to complete recovery of the L1 segment was 162 (43) min in the hypobaric group and 133 (56) min in the plain group ($P > 0.05$). The time until the motor block of the lower extremities regressed (less than 3 on Bromage's scale) was 143 (46) min in the hypobaric group and 150 (45) min in the plain group ($P > 0.05$).

The lowest MAP values during surgery were 74 (9) mm Hg and 81 (10) mm Hg in the hypobaric and plain groups, respectively ($P > 0.05$); the decreases from control values were 21.4% and 13.2% in the hypobaric and plain groups, respectively ($P < 0.05$). Ephedrine was administered for hypotension in five patients in the hypobaric group and none in the plain group ($P < 0.05$). The cephalad spread of analgesia was found to correlate with the maximal decrease in MAP ($P < 0.05$), but not with the decrease in heart rate. The lowest mean heart rate during the study was 49.5 (10.4) beat min^{-1} in the hypobaric group and 55.2 (9.3) beat min^{-1} in the plain group ($P > 0.05$). Bradycardia was treated with atropine in four patients in the hypobaric group.

There were no significant differences in the number of patients who needed intraoperative sedation (two in both groups) or analgesia (three in the hypobaric and two in the plain group) for tourniquet-induced discomfort. One patient (female, 23 yr) in the plain group developed typical postdural puncture headache, which was treated successfully with an extradural blood patch on the 4th day after operation.

COMMENT

The water-diluted bupivacaine solution acted as a strongly hypobaric solution, resulting in a high level of spinal analgesia—T1 on average. In this group, the scatter of spread of analgesia was relatively narrow in all but three patients in whom the cervical nerves were blocked. No major circulatory or ventilatory problems occurred in these patients but, subjectively, the final study patient (pinprick analgesia to C2) felt uneasy and could not breathe deeply.

As a consequence of the rapid and extensive blocks in the hypobaric bupivacaine group, hypotension was more prominent than that in the plain bupivacaine group. We suggest that our hypobaric spinal block technique is unsuitable for patients with cardiovascular disease, even though it is known that, in the case of bupivacaine spinal anaesthesia, the spread of the sympathetic block may not exceed that of the sensory block [5]. The total anaesthetic volume injected in our study was rather large—8 ml of 0.19% bupivacaine. However, the use of 10 ml of bupivacaine–saline solution (baricity virtually unchanged) for spinal anaesthesia has been reported elsewhere [6]. In that study, as well as in others, injected volume of bupivacaine did not seem to have any effect on the block characteristics.

We conclude that subarachnoid injection of hypobaric 0.19% bupivacaine 8 ml produced an unnecessarily extensive spread of spinal analgesia, resulting in considerable hypotension. This makes this hypobaric spinal anaesthesia technique unacceptable for routine clinical use.

ACKNOWLEDGEMENT

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EXTRADURAL ANAESTHESIA IN PATIENTS WITH PREVIOUS LUMBAR SPINE SURGERY

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SUMMARY

We studied prospectively 1381 patients undergoing extradural anaesthesia for total hip or total knee replacement, to determine if extradural anaesthesia can be performed reliably in patients who have had previous lumbar spine surgery. Fifty-two of the 57 patients (91.2%) who had undergone lumbar spine surgery received a successful extradural anaesthetic, and 1307 of 1324 patients without previous back surgery had successful extradural anaesthesia (98.7% success) ($P < 0.0001$). No late complications were observed. Causes for failure of extradural anaesthesia in patients who had previously undergone lumbar spine surgery included technical difficulty (three) and inadequate spread (two).

KEY WORDS

Anaesthetic techniques · extradural, previous spinal surgery.

With the exception of individual case studies [1], there are no reports describing the use of extradural anaesthesia in patients who have undergone previous lumbar spine surgery. In such patients, it is thought that extradural block might entail technical difficulties locating the extradural space, ineffective spread secondary to extradural scar formation, and the possibility of exacerbating back pathology.

Experience with extradural steroids suggests that extradural entry can be obtained in patients who have had previous lumbar spine surgery and that extradural analgesia is therapeutic rather than detrimental.

A prospective study was undertaken to assess the effectiveness of extradural anaesthesia in patients who have had previous lumbar spine surgery.

METHODS AND RESULTS

We studied prospectively 1381 consecutive patients undergoing either total hip or total knee arthroplasty under extradural anaesthesia at one institution. During this period, 22 patients had general and 27 spinal anaesthesia, and were not included for analysis.

Extradural anaesthesia was performed using 17-gauge Tuohy needles inserted one or two interspaces above the site of the previous decompression, using either a midline or a paramedian technique. Bupivacaine 0.75% or 2% lignocaine 15–25 ml with or without adrenaline in a concentration of 1:200000 were used in all subjects. Extradural opioids were not given routinely during operation, but were used in several patients with previous decompressive laminectomy.

Failure was defined as inability to locate the extradural space, inadequate anaesthesia following extradural injection or dural puncture with the 17-gauge Tuohy needle. All patients with failed extradural anaesthesia subsequently received general, spinal or repeated extradural anaesthesia. There were no neurological sequelae in any patients and no clinically significant exacerbation of lumbar radiculopathy in the patients who had undergone previous spine surgery.

Differences between groups were analysed using unpaired t test or chi-square analysis (table I). Extradural anaesthesia was performed successfully in 1307 of 1324 patients without previous lumbar spine surgery (failure rate 1.3%) and in 52 of 57 patients with previous spine surgery (failure rate 8.8%) ($P < 0.0001$).

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TABLE I. *Success rates of extradural anaesthesia with and without lumbar spine surgery (mean (SD)).* ***$P < 0.0001$

	Previous lumbar spine surgery ($n = 57$)	No previous back surgery ($n = 1324$)
Age (yr)	63.1 (13.8)	63.2 (13.4)
Height (cm)	163.8 (18.8)	164.2 (11.4)
Weight (kg)	77.0 (17.9)	72.5 (16.5)
Sex (M/F)	32/25	492/831
ASA	2.1 (0.678)	2.1 (0.686)
Osteoarthritis	43	987
Rheumatoid arthritis	1	138
Others	13	199
Success rate	52 (91.2%)	1307 (98.7%)***
Failure rate	5 (8.8%)	17 (1.3%)
Repeat anaesthesia		
General	2	8
Spinal	3	4
Repeat extradural	0	5

COMMENT

This study has demonstrated that extradural anaesthesia can be used successfully in patients with previous spinal surgery, but that additional technical difficulties may be encountered [1]. The success rate of extradural anaesthesia in 98.7% of patients is surprising, as the majority were elderly and suffering from osteo- or rheumatoid arthritis [2]. Failure rates for extradural anaesthesia have been reported to range from 1 to 10%, depending on the technique and surgical setting [3, 4]. The relatively high success rate reported here may reflect the generous dose of anaesthetic used and the familiarity of the anaesthetists with extradural anaesthesia in the arthritic patient. At this institution, 80% of all surgery is performed under regional anaesthesia so all anaesthetists are familiar with extradural techniques in this patient population.

Two patients exhibited inadequate anaesthesia in the lumbosacral segments, presumably because of scar formation preventing extradural spread of the local anaesthetic to the lumbosacral nerve roots. Both developed anaesthesia to the upper thoracic dermatomes. One of these patients had had three previous laminectomies. To circumvent this difficulty, large volumes of more concentrated local anaesthetic with adrenaline, opioids, or both [3] may be used to intensify neural block. Increased CSF uptake of local anaesthetic, adrenaline or opioids may augment the spinal cord site of action. Alternatively, small repeated doses may provide a more intense local block.

Extradural injection close to the surgical incision may be complicated by lack of landmarks, spinal stenosis immediately above the fusion or decompression [5], or tethering of the dura to the ligamentum flavum by scar formation [6]. For these reasons, extradural anaesthesia should be attempted one, or preferably, two interspaces above the site of previous lumbar surgery to avoid dural puncture or failed extradural block. With this approach, successful extradural entry was obtained in 54 of 57 patients and no inadvertent subarachnoid punctures resulted. Moreover, two of the patients in whom technical difficulty was encountered had back pathology (ankylosing spondylitis and spondylo–epiphyseal dysplasia) in which lumbar extradural anaesthesia is almost impossible.

Although extradural anaesthesia was performed successfully in patients with previous lumbar spine surgery, there was increased difficulty and failures were observed. However, patients who may benefit from extradural anaesthesia or postoperative extradural analgesia should not be denied this technique because of previous lumbar spine surgery.

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DOUBLE-BLIND COMPARISON OF TOPICAL LIGNOCAINE–PRILOCAINE CREAM (EMLA) AND LIGNOCAINE INFILTRATION FOR ARTERIAL CANNULATION IN ADULTS

M. SMITH, B. M. GRAY, S. INGRAM AND D. A. JEWKES

SUMMARY

In a double-blind, double-dummy study, the efficacy of topical 5% EMLA cream was compared with that of lignocaine infiltration in alleviating the pain of arterial cannulation. Forty unpremedicated adults were allocated randomly to four groups to receive EMLA cream alone, EMLA and 0.9% saline infiltration, EMLA and 1% lignocaine infiltration or placebo cream and 1% lignocaine infiltration. Following arterial cannulation, pain was assessed by the patient using a visual analogue score and by an independent observer using a four-category verbal rating score. Significantly lower pain scores were observed in all patients receiving EMLA compared with those receiving placebo cream and lignocaine infiltration by both patient ($P < 0.01$) and observer ($P < 0.001$) assessments. There were no significant differences between the three EMLA groups.

KEY WORDS

Anaesthetics, local: lignocaine, topical lignocaine–prilocaine

EMLA 5% has been shown to produce dermal anaesthesia before skin puncture during i.v. cannulation in adults [1, 2] and children [3–5]. Studies have demonstrated that EMLA should be applied for a minimum of 45 min before skin puncture [2]. Any local reactions are of minor nature, transient and resolve without treatment [6].

There have been no double-blind studies on the use of EMLA cream during arterial cannulation, which may be undertaken before induction of anaesthesia or in awake patients in the Intensive Care Unit; infiltration of the skin with lignocaine is the method of analgesia usually chosen. However, infiltration itself may be painful and may not provide adequate analgesia. Premedicated patients may be able to tolerate such manoeuvres but, in the unpremedicated patient, arterial cannulation may be an unpleasant experience.

This study was designed to assess the efficacy of EMLA cream to alleviate the pain of arterial cannulation in unpremedicated adults and to compare its analgesic action with that of infiltration with lignocaine.

METHODS AND RESULTS

Forty adult patients were investigated in the study, for which local Ethics Committee approval had been granted. Neurosurgical patients who would not normally receive premedication, but who required arterial cannulation, were included and informed, written consent was obtained from each. Any patient was excluded with a decreased conscious level or a neurological deficit in the upper limbs.

The patients were allocated randomly to one of four groups: EMLA cream only; EMLA and infiltration of 0.9% saline; EMLA and infiltration of 1% lignocaine; placebo cream and infiltration of 1% lignocaine. At least 60 min before induction of anaesthesia, one of the authors (B.G.) applied either one tube of EMLA or a similar volume of

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placebo cream to appropriate patients over both radial arteries and covered it with a Tegaderm (3M) occlusive dressing. E45 cream was used as the placebo and had similar appearances to EMLA when placed under the occlusive dressing.

On arrival of the patient in the anaesthetic room, the occlusive dressings and cream were removed. In those patients who were to receive infiltration, a 2-ml syringe containing either 0.9% saline or 1% lignocaine was prepared and infiltration of the skin carried out using approximately 0.2–0.3 ml of the appropriate agent injected intradermally using a 25-gauge needle. Arterial cannulation using a 20-gauge cannula (Abbocath) was performed 2 min after infiltration or immediately after removal of the cream in the group receiving EMLA only. Following cannulation, a visual analogue scale (VAS) was completed by the patient to quantify the discomfort experienced during the procedure. This was scored also by an independent observer using the following simple four-category verbal rating scale (VRS): 1 = no response from patient; 2 = mild facial grimace; 3 = verbal response; 4 = withdrawal of hand. The operator and observer were common to all patients and neither was aware of the group to which the patient was assigned.

VAS and VRS data were tested using the Kruskal–Wallis one-way analysis of variance by ranks and the Mann–Whitney U test.

The mean (range) age of the patients was 48.3 (22–69) yr; there was no difference in age or sex ratio between the groups.

Figure 1 shows individual patient VAS and VRS data and the mean values for each group. The VAS scores were significantly lower ($P < 0.01$) in the EMLA groups (groups 1–3) than the placebo cream–lignocaine infiltration group (group 4). There was no significant difference between the VAS scores in the three EMLA cream groups. Similarly, the VRS scores in groups 1, 2 and 3 were similar and significantly lower than those in group 4 ($P < 0.001$).

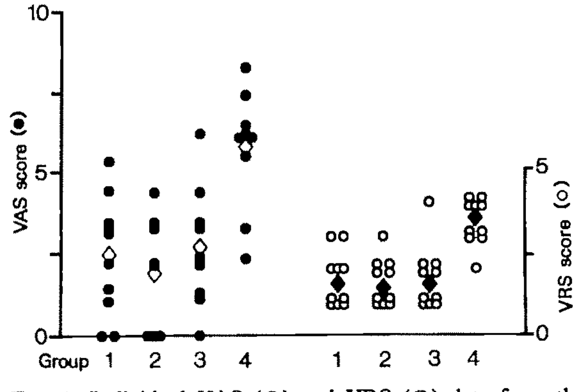

FIG. 1. Individual VAS (●) and VRS (O) data from the patients in each of the four groups. Group 1 = EMLA alone; group 2 = EMLA and 0 9% saline; group 3 = EMLA and 1% lignocaine; group 4 = placebo and 1% lignocaine. The mean VAS (◇) and VRS (◆) for each group are also shown.

No serious side effects were noted. Mild blanching was observed in eight patients in the EMLA groups and two in the placebo group, but this settled within 30 min in all patients. Erythema related to the occlusive dressing was observed in three patients.

COMMENT

In adults, the eutectic mixture of lignocaine and prilocaine bases (EMLA) has been shown to penetrate intact skin [1, 6] and it is used widely for pain-free venepuncture in adults [1, 2] and children [3–5]. This study has demonstrated that EMLA cream is also useful for alleviating pain during arterial cannulation in unpremedicated adults.

Both patient VAS and observer VRS scores were significantly lower in the patients treated with EMLA cream. It has been demonstrated that EMLA was equally as effective as infiltration of lignocaine in alleviating the pain of venepuncture in children [4], but we have shown that, during arterial cannulation in adults, EMLA is more effective than infiltration of lignocaine. There is no obvious explanation for this difference, but fear of needles may cause children to overestimate the pain of cannulation after EMLA cream.

Previous studies have demonstrated that the EMLA becomes effective 45 min after application in adults [2], although 60 min is necessary in children [5]. The cream was applied at least 60 min before cannulation in this study, and good analgesia was obtained in all subjects. Analgesia has been observed for up to 300 min after application [3].

Patients in the EMLA cream groups who also had infiltration of the skin (with either saline or lignocaine) had similar VAS and observer scores, confirming that skin infiltration itself did not contribute to the analgesic effect.

The use of EMLA is associated with minimal side effects [6], and temporary blanching on removal of the dressings is the only problem reported regularly. In our study, EMLA cream did not cause any serious skin reactions; blanching which settled within 30 min was noted in only 10 of the 40 patients studied.

Some workers have shown that analgesic premedication has no effect on the pain reported during venepuncture [6], in contrast with other reports [3]. All patients in our study received no premedication and therefore the analgesic effects may be attributed to EMLA cream.

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PLASMA CONCENTRATIONS OF BUPIVACAINE AFTER STELLATE GANGLION BLOCK USING TWO VOLUMES OF 0.25% BUPIVACAINE PLAIN SOLUTION

P. A. J. HARDY AND N. E. WILLIAMS

SUMMARY

Plasma concentrations of bupivacaine were measured in patients after stellate ganglion block using either 10 or 20 ml of 0.25% plain solution. The mean peak concentrations were greater in the larger volume group, but this was not statistically significant. From 30 min after injection, there was a significantly greater plasma concentration in the larger volume group. The concentrations approached the limit of detection in the smaller volume group at 2 h after block.

KEY WORDS

Anaesthetic techniques, regional: stellate ganglion block. Anaesthetics local: bupivacaine

Sympathetic ganglion block is used in diagnosis and treatment of several chronic painful conditions. The cervicothoracic sympathetic chain may be blocked in the neck using the so-called "stellate ganglion block". Injection is made into the areolar tissue anterior to the precervical fascia, using volumes of up to 20 ml depending on the extent of sympathetic block required [1].

Significant absorption of local anaesthetic may occur from the site of injection. The plasma concentrations of local anaesthetic produced after procedures performed in patients with chronic pain may be important, because i.v. injection of local anaesthetic has been used for treatment of several such conditions [2]. It is possible, therefore, that this may account for the analgesia obtained after sympathetic block in chronic pain [1].

A prospective study was performed in patients receiving stellate ganglion block for treatment of chronic pain to assess plasma concentrations produced after use of two volumes of injectate—10 ml and 20 ml.

METHODS AND RESULTS

The study was approved by the District Ethics Committee and informed consent was obtained from patients. Venous blood samples of 2–5 ml were obtained from an indwelling cannula before and at 5, 10, 20, 30, 60, 90 and 120 min after the stellate block was performed. Two groups of patients were studied: five patients receiving 10 ml and five receiving 20 ml of 0.25% plain bupivacaine. The standard anterior paratracheal approach to the sympathetic chain at C6 was used for all blocks. The carotid sheath on the appropriate side was located and retracted laterally using one hand. A needle was inserted lateral to the trachea to contact the anterior surface of the cervical vertebral body. The needle was withdrawn 0.5 cm to lie anterior to the precervical fascia. After a negative aspiration test for blood or CSF, the appropriate volume was injected.

Blood was centrifuged and the separated plasma frozen and sent to the Department of Biochemistry, St Albans City Hospital for assay for bupivacaine by high pressure liquid chromatography on reverse phase with u.v. detection at 205 nm. This technique has a limit of detection of 0.05 $\mu g\ ml^{-1}$.

Statistical analysis using the Mann–Whitney *U* test was performed using an Amstrad PCW 9512 with the "Oxstat" package.

Plasma concentrations of bupivacaine reached peak values at 10 min in the smaller volume and

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TABLE I. *Plasma concentration* (*μg* ml^{-1}) *of 0.25% bupivacaine at various times after injection of 10 ml or 20 ml to individual patients.* **Significant difference between 10- and 20-ml groups*

Patient No.	Time after injection (min)							
	0	5	10	20	30	60	90	120
10 ml injected								
1	—	0.23	0.39	0.18	0.2	0.15	0.09	—
2	—	0.11	0.11	0.22	0.28	0.22	0.12	0.08
3	—	0.36	0.41	0.41	0.28	0.22	0.13	0.08
4	—	0.3	0.36	0.41	0.36	0.21	0.16	—
5	—	0.11	0.44	0.33	0.27	0.22	0.16	0.12
Mean	—	0.22	0.34	0.31	0.27	0.20	0.13	0.06
20 ml injected								
1	—	0.17	0.36	0.62	0.73	0.42	0.29	0.14
2	—	0.21	0.43	0.4	0.39	0.35	0.32	0.19
3	—	0.08	0.24	0.34	0.4	0.29	0.27	0.2
4	—	0.56	0.6	0.62	0.51	0.4	0.26	0.19
5	—	0.17	0.3	0.36	0.31	0.33	0.3	0.28
Mean	—	0.24	0.39	0.47	0.47	0.36	0.29	0.2
U	—	11	12	6	1*	0*	0*	0*

20 min in the larger volume group (table I). The mean peak value was greater in the larger volume group, but this difference was not statistically significant. The concentrations decreased over 120 min, to around or below the limits of detection in the 10-ml group. There was a statistically higher plasma concentration in the larger volume group, from 30 min to 120 min. The plasma concentration did not approach toxic values in any patient.

COMMENT

The concentrations of local anaesthetic obtained after stellate ganglion block have not been reported previously [3]. The concentrations obtained after either 10 or 20 ml of 0.25% bupivacaine in this study were substantially less than the reported toxic concentration of 1.5 μg ml^{-1} [3]. Peak concentrations were obtained in both groups 10–20 min after injection.

The reported time to maximal increase in skin temperature in the hand after stellate ganglion block with 0.5% bupivacaine plain solution is 30 min [4]. The peak plasma concentration in the 20-ml group was maintained up to this period. It is possible, therefore, that part of the effects observed after stellate ganglion block may be related to systemic local anaesthetic and not sympathetic block.

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COMPARISON OF FOUR PULSE OXIMETERS: EFFECTS OF VENOUS OCCLUSION AND COLD-INDUCED PERIPHERAL VASOCONSTRICTION

J. A. LANGTON, D. LASSEY AND C. D. HANNING

SUMMARY

The ability of four pulse oximeters (the Ohmeda 3700, Nellcor N100 and N200 and the Datex Oscar) to detect hypoxaemia was determined in the presence of venous obstruction and cold-induced peripheral vasoconstriction. Significant increases in detection time for hypoxaemia were found in both cases. There were no significant differences in detection time between the instruments, although the Ohmeda 3700 displayed smaller values of Sa_{O_2} *under certain conditions. Peripheral vasoconstriction was induced using three differing methods which gave differing results, thus emphasizing the importance of methodology in assessments of pulse oximetry.*

KEY WORDS

Equipment · pulse oximeters

Pulse oximetry is rapidly being adopted as a standard in clinical monitoring [1]. It is clear that instruments from different manufacturers vary in their ability to function under adverse conditions, in particular poor peripheral perfusion and motion artefact. A previous study from this department [2] found that venous occlusion and cold-induced peripheral vasoconstriction impaired the performance of some of the pulse oximeters under test, so that episodes of hypoxaemia were not detected despite apparently normal functioning. The present study extends the evaluation to further oximeters, including one with ECG linkage, and evaluates different methods of inducing vasoconstriction.

METHOD AND RESULTS

Ethics Committee approval was obtained; 20 healthy subjects gave informed consent to participate in the study.

The Ohmeda 3700, Nellcor N100, Nellcor N200 (which has an ECG linkage) and the Datex Oscar were evaluated. All the pulse oximeters tested were used in the default mode set at the minimum time for averaging. The subjects rested on a couch and the oximeter probes were applied in random order to the fingers of the left hand, the thumb not being used. The probe of an Ohmeda Biox III oximeter was applied to the subject's ear lobe as a source of reference data and for safety purposes. The ECG leads of the Nellcor N200 were applied in the CM5 configuration. The oxyhaemoglobin saturation (Sa_{O_2}) outputs from the instruments, calibrated according to the manufacturer's instructions, were recorded on a W & W electronic 400 series (model 406) six-channel chart recorder with a thermowriting system.

All experiments were conducted in an air-conditioned laboratory with a constant room temperature of 23–25 °C.

When stable readings were obtained, a 5-min period was recorded for baseline values and two episodes of hypoxaemia were induced, the subject inhaling a mixture of 10% oxygen in nitrogen from a pre-filled Douglas bag via a closely fitting non-rebreathing mask with normal tidal ventilation. Each episode of hypoxaemia lasted 2 min and was terminated if the reference instrument indicated that Sa_{O_2} had decreased to $< 75\%$. The subjects breathed room air for 3 min between episodes. The time from the first breath of hypoxic gas to the first decrease in the Sa_{O_2} record (detection time) and the minimum Sa_{O_2} were noted.

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Venous occlusion

A standard sphygmomanometer cuff was applied to the upper arm and inflated to 40 mm Hg to induce venous congestion. Five minutes later, two further episodes of hypoxaemia were induced as before.

Vasoconstriction

The test arm was cooled using three different methods on three separate occasions. First, the subject's forearm was surrounded by a water-filled plastic envelope that had been cooled overnight in a domestic refrigerator to 4 °C. The oximeter probes were allowed to protrude from the envelope to avoid direct cooling. Five minutes later, 12 episodes of hypoxaemia were induced at 5-min intervals as the cooling progressed; the final two episodes were included in the final analysis. The total period of induced vasoconstriction was 60 min. Second, the subject's forearm was laid on a water-filled bag which had been cooled overnight to 4 °C. A second cold bag was then laid across the arm so that the subject's hand and fingers protruded. The sequence of episodes of hypoxaemia was repeated as above. Third, the subject's forearm was wrapped between two flat coils of a blood warmer (Fenwal) held gently in place with a crepe bandage. Ice cold water was circulated through the coils using a roller pump. Thermocouples were inserted into the circuit to measure the temperature of the water entering and leaving the coils. The subject's hand temperature was measured continuously using an Edale digital thermometer with the temperature probe applied to the inner aspect of the index finger. The subject's forearm was cooled to 26 °C, at which point the roller pump was stopped. Two episodes of hypoxaemia were induced as before.

Differences between the instruments were assessed by analysis of variance and the Wilcoxon signed rank test as appropriate.

One subject was found to have markedly prolonged control and test detection times of 57 and 116 s, respectively, and a reduced skin temperature of 26.8 °C indicating pre-existing vasoconstriction. Her results were excluded from the detailed analysis. She was a healthy 20-yr-old recovery room nurse, with no symptoms of peripheral vascular disease or Raynaud's disease.

Venous congestion significantly prolonged the detection time in all oximeters compared with

TABLE I. *Detection time and minimum* Sa_{O_2} *for episodes of induced hypoxaemia during venous occlusion and vasoconstriction (all three methods combined) for each of the pulse oximeters. Mean* (SEM) *[range] (Wilcoxon signed rank test).**P < *0.05*; **P < *0.01*

	Detection time (s)		Minimum Sa_{O_2} (%)	
Instrument	Control	Test	Control	Test
Venous occlusion ($n = 13$)				
Datex Oscar	36.2 (2.3)	49.1 (5.7)*	86.48 (0.73)	85.3 (0.87)
	[22–50]	[24–96]	[78–94]	[78–93]
Nellcor 200	34.3 (2.5)	47.6 (5.5)*	86.4 (0.94)	84.1 (0.87)
	[24–53]	[24–84]	[78–94]	[77–91]
Ohmeda 3700	36.5 (2.1)	48.8 (4.8)**	86.28 (0.8)	84.9 (0.8)
	[24–53]	[22–75]	[78–92]	[78–93]
Nellcor 100	31.1 (1 9)	42.6 (5.2)**	86.4 (0.9)	86.23 (0.79)
	[24–46]	[19–75]	[79–92]	[76–91]
Biox III	31.9 (2.9)	30.3 (3.2)	87.8 (0.7)	86.5 (0.64)
	[14–56]	[19–52]	[80–94]	[80–92]
Vasoconstriction ($n = 15$)				
Datex Oscar	38.5 (3.2)	76.2 (10)**	86.5 (0.6)	86.4 (0.89)
	[22–67]	[29–168]	[78–94]	[81–92]
Nellcor 200	37.8 (2.6)	67.8 (8.3)**	85.7 (0.76)	85.9 (0.87)
	[24–58]	[29–146]	[78–92]	[76–92]
Ohmeda 3700	37.2 (2.8)	66.7 (8.2)**	86.3 (0.82)	81.1 (0.94)
	[24–62]	[24–161]	[78–94]	[68–94]
Nellcor 100	36.1 (2.9)	66.4 (8.5)**	85.8 (0.88)	85.5 (0.96)
	[24–62]	[26–149]	[79–93]	[77–94]
Biox III	32.9 (2.9)	32.0 (4.7)	85.7 (0.76)	85.9 (0.87)
	[14–58]	[17–86]	[78–94]	[81–94]

control ($P < 0.05$) (table I). There were no differences between the oximeters with respect to detection time.

The combined results of all three methods of producing peripheral vasoconstriction showed a significant prolongation of detection time compared with control values ($P < 0.01$). There were no differences between the oximeters.

Both the control and test detection times for the pump method of producing peripheral vasoconstriction were significantly longer than the other two methods.

The Ohmeda 3700 gave significantly smaller values of Sa_{O_2} compared with the other oximeters ($P < 0.05$).

COMMENT

The purpose of a pulse oximeter is rapid, accurate and reliable detection of hypoxaemia. It is inevitable that under certain circumstances a pulse wave is not detectable, and the instruments should alert the user immediately. All the oximeters in the present study functioned reliably and accurately, although with a marked prolongation of detection time. This is in contrast with our previous study [2] in which one oximeter failed to detect hypoxaemia despite apparently normal functioning.

The prolongation of detection time is clinically important, as equivalent degrees of venous congestion and vasoconstriction may occur in practice. The possibility of delayed detection (and thus correction of hypoxaemia) lends weight to the necessity of monitoring inspired gas concentrations and adequacy of ventilation.

We assessed three different methods of surface cooling to induce peripheral vasoconstriction. They may not reproduce exactly the conditions found in clinical practice, in that they do not produce concomitant reductions in cardiac output, but they are simple, non-invasive and applied easily to volunteers. The envelope and bag methods are convenient and applied easily to the subject's arm, but there was no control over the rate of cooling of the arm. The pump method was devised to give controllable surface cooling, but probably introduced some venous occlusion, as the detection times were significantly greater than the other methods. A future modification to this technique would be to remove the coils from the subject's arm when the cooling was complete and so avoid venous occlusion.

The Ohmeda 3700 was common to the present and previous study [2]. The control and test detection times were approximately twice as long in the previous study as in the present, although the methodology was identical. There are two explanations for the differences. First, the envelope used in the previous study may have been filled to such a degree that it also produced venous obstruction in a manner similar to the pumped method in the present study. Second, the subjects may have had poor peripheral perfusion before cooling started. In the present study one subject, who was excluded from the analysis, was found to have a finger temperature of 26.8 °C at the start of the study. Her control and test detection times were 57 s and 116 s, respectively—that is, of the same order of magnitude as values found in the previous study.

In contrast with the previous study [2], none of the oximeters failed, and they were comparable in their responses to venous congestion and vasoconstriction, although the Sa_{O_2} values displayed by the Ohmeda 3700 were consistently less than those from the other instruments. This has been noted by other workers [2, 3].

New oximeters are being introduced frequently and it is important that their ability to perform reliably under adverse conditions is tested. The present study suggests that there have been improvements in the quality of the microprocessor software since the previous study. It also emphasizes the need for consistent methods in inducing vasoconstriction and the importance of avoiding inadvertent venous congestion. ECG linkage is used by some pulse oximeters to scan for a pulse wave during a short time period following the R wave on the ECG. It is thought that this may be helpful in conditions of poor peripheral perfusion, but in this study no difference was found between the instrument with ECG linkage and those without.

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CRITICAL VOLUME FOR PULMONARY ACID ASPIRATION: REAPPRAISAL IN A PRIMATE MODEL

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SUMMARY

We have studied, in the monkey, the critical volume for the production of severe pneumonitis following pulmonary aspiration of gastric contents. Aspiration of 0.4 ml kg^{-1} and 0.6 ml kg^{-1} at pH 1 produced mild to moderate clinical and radiological changes, but no deaths. Aspiration of 0.8 ml kg^{-1} and 1.0 ml kg^{-1} at pH 1 was associated with an increasingly severe pneumonitis. At 1.0 ml kg^{-1}, 50% of the animals died—a mortality rate considerably less than that reported previously in animal studies. If these results were to be extrapolated to humans, the critical volume for severe aspiration could be increased from 25 ml to 50 ml (0.8 ml kg^{-1}), considerably reducing the percentage of patients perceived to be "at risk".

KEY WORDS

Anaesthesia. obstetric. Complications. pulmonary aspiration.

METHODS AND RESULTS

The study was conducted following approval by the University of Natal Ethics and Professional Standards Committee. Twenty-four juvenile monkeys (*Cercopithecus aethiops*) (mean (SD) weight 2.82 (0.86) kg) were allocated randomly to four groups according to the volume of gastric aspirate administered. Animals were anaesthetized initially with ketamine 30 mg i.v., following which an orogastric tube was inserted and gastric contents aspirated. Aspirate was obtained from several animals on the morning of each study day and was pooled, and homogenized manually. The pH of the aspirate was measured and adjusted to pH 1 by addition of hydrochloric acid: whilst the aspirate was stirred continually using a magnetic stirrer, three to six drops of hydrochloric acid (HCl) 1 mol litre^{-1} (pH 0.5) were added until the pH of the aspirate was approximately 1. Thereafter, one to six drops of HCl 0.1 mol litre^{-1} (pH 1.10) were added to bring the aspirate to precisely pH 1.

Monkeys were weighed and examined clinically for signs of infection or cardiorespiratory disease. Any animal with a heart rate > 140 beat min^{-1} or a ventilatory frequency > 40 b.p.m. was excluded from the study. Following this examination, the trachea was intubated and the position of the tube verified both clinically and by chest radiography, the latter being used also to exclude pulmonary disease. Animals were allocated randomly to receive gastric aspirate of differing volumes: group I 0.4 ml kg^{-1}; group II 0.6 ml kg^{-1}; group III 0.8 ml kg^{-1}; group IV 1.0 ml kg^{-1}. Aspirate was drawn up into a syringe using a 21-gauge needle which was instilled, by the same investigator (D.M.R.), into the lumen of the tracheal tube. Animals were allowed to breathe spontaneously during pulmonary instillation of gastric aspirate. Immediately upon completion of injection of aspirate, the lungs were ventilated for a period of 1 min with a tidal volume of 20 ml kg^{-1} using a Starling pump, to ensure widespread distribution of the aspirate. Following ventilation, the tracheal tube was removed and animals transferred to an observation room for 6 h. During the observation period, anaesthesia was main-

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TABLE I. *Mean (SD) percentage changes from a baseline of 100% of ventilatory frequency (VF) and heart rate (HR) for each volume of aspirate at various times during the post-aspiration observation period*

Volume of aspirate		15 min	30 min	60 min	2 h	4 h	6 h
0.4 ml kg^{-1}	VF	186 (79)	194 (100)	176 (69)	169 (59)	162 (42)	153 (37)
	HR	108 (29)	119 (22)	116 (16)	111 (25)	107 (19)	121 (23)
0.6 ml kg^{-1}	VF	122 (21)	120 (17)	133 (45)	139 (41)	144 (49)	132 (56)
	HR	92 (10)	98 (15)	103 (12)	103 (23)	97 (27)	101 (30)
0.8 ml kg^{-1}	VF	145 (69)	165 (100)	166 (120)	188 (147)	181 (87)	165 (84)
	HR	109 (23)	106 (28)	98 (19)	96 (20)	90 (21)	95 (18)
1.0 ml kg^{-1}	VF	164 (100)	170 (100)	137 (75)	155 (120)	140 (124)	119 (97)
	HR	109 (20)	99 (18)	91 (18)	84 (31)	93 (24)	94 (41)

tained with diazepam supplemented with ketamine given i.v. via a glucose–saline infusion of 5 drops kg^{-1} min^{-1} (paediatric giving set—60 drops ml^{-1}). During the period after aspiration, temperature, heart rate, ventilatory frequency, degree of cyanosis (mild, moderate, severe) and presence or absence of wheezing on auscultation were noted. Observers were unaware of the volume of aspiration. Observations were made at 5-min intervals for 30 min, at 15-min intervals for the next 90 min and every 30 min for the remaining 4 h. Chest radiography was repeated at 2 and 6 h after aspiration.

Six hours after aspiration, monkeys were allowed to recover, and were housed in separate cages for the next 24 h. Food and water was provided *ad libitum* and animals observed for signs of respiratory distress. Euthanasia was permitted if severe distress occurred, but this was not required for any animal. Chest radiography and clinical examination were repeated daily under ketamine anaesthesia until recovery.

Any animal that died during the study period underwent immediate postmortem (A.M.) during which the lungs and trachea were removed for subsequent histological examination. Lungs were fixed in formalin, and subsequent paraffin-embedded histological sections, stained with haematoxylin and eosin, were examined under light microscopy.

Before the definitive study, two additional monkeys were subjected to aspiration of dionosil 1 ml kg^{-1}, pH 3.8 to demonstrate the efficacy of the methodology.

None of the animals died in either the 0.4- or 0.6-ml kg^{-1} groups. One animal died in the 0.8-ml kg^{-1} group 12 h after aspiration, and three animals died in the 1-ml kg^{-1} group. In this last group, two animals died within 2 h of aspiration and the third animal died unexpectedly on day 7 after aspiration, following apparent recovery.

While some degree of cyanosis, tachypnoea and tachycardia were observed in most animals immediately after aspiration, clinical signs varied in severity (table I). In some, bradycardia, bradypnoea, or both, developed. The two early deaths in group IV were associated with severe cyanosis and pulmonary oedema. Radiological changes of patchy alveolar shadowing and consolidation were mild in those animals receiving 0.4 and 0.6 ml kg^{-1} and increased in severity with increasing volumes of aspirate. Histological examination of the animals which died revealed the presence of acute inflammatory cell infiltrate, intra-alveolar haemorrhage, pulmonary oedema and congestion.

COMMENT

Early experimental work demonstrated the importance of the pH of gastric contents which were aspirated, the severity of pneumonitis being related to increased acidity of aspirate [1]. In 1974 Roberts and Shirley "arbitrarily defined the patient at risk as that patient with at least 25 ml of gastric juice (0.4 ml kg^{-1}) of pH below 2.5 in the stomach at delivery" [2]. This "at risk" concept placed a high percentage of mothers in danger of severe pneumonitis if aspiration should occur and led to the extensive use of measures to reduce the consequences of aspiration. Such measures included administration of antacid throughout active labour and administration of H_2-receptor blockers and agents which increased lower oesophageal sphincter tone. Whilst there has been a paucity of experimental work to validate the "at risk" values, the need for extensive prophylaxis was emphasized further in a study by James and colleagues, who demonstrated 90% mortality following aspiration of 0.4 ml kg^{-1} at pH 1 in the rat [3]. However, in a preliminary study into the early physiological changes following aspiration of 0.4 ml kg^{-1} at pH 1, in a primate model, none of the animals died [4]. Subsequent review of the literature revealed that the initial at risk concept as outlined by Roberts and Shirley was based on a single experiment in the monkey which was published eventually in 1980 [5]. This single experiment involved the instillation of the entire 0.4 ml kg^{-1} into the right main bronchus. This might be considered analogous to tracheal aspiration of 0.8 ml kg^{-1}, thus invalidating the conclusions.

Whilst the acidity of the aspirate is accepted as contributing significantly to the severity of the pulmonary changes, the role of volume of aspirate remains unclear. None of the animals in groups I and II in our study died—a result which is at variance with the high mortality reported previously in a rat model [3]. Our study has demonstrated, therefore, that in the monkey, the volume of aspirate required to produce severe pneumonitis with a significant mortality is at least 0.8 ml kg^{-1}, and that aspirates up to 0.6 ml kg^{-1} do not cause severe pneumonitis. A criticism of our study may be that not all the aspirate may have entered the tracheobronchial tree. Whilst some workers have performed tracheotomy to ensure correct placement of aspirate, in our study every precaution was taken to exclude loss of aspirate from the trachea. Tracheal tubes were tightly fitting, animals were not allowed to cough vigorously following instillation of the aspirate, and the pharynx was inspected immediately after aspiration for signs of aspirate. In addition, the two control animals showed that radio-opaque aspirate was distributed well throughout the lung fields.

A further criticism of our study is that the clinical observations were imprecise. Clinical observations of heart rate, ventilatory frequency, cyanosis and dyspnoea varied considerably between animals and these measurements did not correlate with increasing volumes of aspirate (table I). In addition, with the larger volumes of aspirate, the associated severe hypoxia was accompanied by bradycardia (heart rate < 100 beat min^{-1}). We feel that the small numbers of animals studied and the variability and subjectivity of the observations make the clinical observations difficult to interpret. In addition, the animals were allowed to breathe air spontaneously during the observation period, which is unlikely in clinical practice. A separate study to examine haemodynamic and respiratory changes by invasive or non-invasive monitoring after aspiration may be required. Finally, the aspirate instilled was not devoid of particulate matter, and this may have influenced the response. However, the instillation of large particles was prevented by producing an evenly homogenized sample drawn through a small, 21-gauge needle.

Extrapolation of our data suggests that the critical volume for acid aspiration can be increased to at least 50 ml of pH 1 (0.8 ml kg^{-1}). Such a change reduces considerably the percentage of patients deemed to be at risk from aspiration and would allow clinicians to place less emphasis on attempts to reach small, often unobtainable, residual gastric volumes. We wish to emphasize, however, that every effort must still be made to ensure that acidic gastric contents are neutralized. The results of this study not only pave the way for less stringent attempts towards reducing gastric volume, but also the possibility of administering a small amount of clear fluid to the pregnant patient in labour. Recent work by Maltby and colleagues has already demonstrated the gastric emptying properties of a preoperative drink in the non-pregnant ambulant day patient and such a study should now perhaps be undertaken in the pregnant patient [6].

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SITE OF ACTION OF FENTANYL IN INHIBITING THE PITUITARY–ADRENAL RESPONSE TO SURGERY IN MAN

G. M. HALL, S. LACOUMENTA, G. R. HART AND J. M. BURRIN

SUMMARY

To determine the site of action of fentanyl in attenuating the pituitary–adrenal response to surgery, we have measured serum concentrations of cortisol and growth hormone during and after a standardized surgical procedure in two groups of patients. One group received fentanyl 15 μg kg⁻¹ i.v. immediately before the start of surgery; a second group received fentanyl 15 μg kg⁻¹ i.v. together with corticotrophin releasing factor 100 μg i.v., growth hormone releasing hormone 100 μg i.v. and arginine vasopressin 10 units i.m. The concomitant administration of the releasing factors with the opioid resulted in a significantly greater serum concentration of cortisol 30, 60, 120 and 240 min after surgery commenced, compared with the group which received fentanyl alone. Similarly, the growth hormone response in the combined group was significantly greater than in the fentanyl-alone group 30 min after the start of surgery. We conclude that the inhibitory effect of fentanyl on surgically-induced secretion of pituitary hormone was mediated directly or indirectly via the hypothalamus.

KEY WORDS

Analgesics, opioid: fentanyl Hormones.

Fentanyl is used commonly in anaesthetic practice. In high doses (> 50 μg kg^{-1} i.v.), it prevents completely the pituitary hormonal response to pelvic and upper abdominal surgery [1]. We have shown that doses of fentanyl as small as 15 μg kg^{-1} i.v. reduce the adrenocorticotrophic hormone (ACTH), β-endorphin, cortisol and growth hormone (GH) responses to pelvic surgery [2]. It is not known if these effects of fentanyl are mediated via the hypothalamus or the pituitary. In the present study, we have investigated the site of action of fentanyl 15 μg kg^{-1} during surgery by the concomitant use of the hypothalamic releasing factors, growth hormone releasing hormone (GHRH), corticotrophin releasing factor (CRF) and arginine vasopressin (AVP).

METHODS AND RESULTS

We studied 12 healthy patients undergoing fallopian tubal surgery. They were not receiving any medication. The patients were allocated randomly to receive either fentanyl or fentanyl together with hypothalamic releasing factors. The study was approved by the Hospital Ethics Committee; the nature of the investigation was explained to the patients and written consent obtained.

All patients were premedicated orally with diazepam 10 mg 2 h before surgery. On arrival of the patient in the anaesthetic room, a central venous catheter was inserted percutaneously via an antecubital fossa vein for administration of drugs and fluids and collection of blood samples. After the patient had rested for 10 min, a control blood sample was obtained. Anaesthesia was induced in all patients with thiopentone 4–5 mg kg^{-1}, the trachea was intubated after administration of pancuronium 0.1 mg kg^{-1}, and the lungs ventilated with 70% nitrous oxide in oxygen. Fentanyl 15 μg kg^{-1} i.v. was given to all patients just before surgery commenced. In those patients ($n = 6$) who received the hypothalamic releasing factors, human CRF 100 μg and GHRH 1–29 100 μg (Bachem Laboratories, Torrance, U.S.A.) were given i.v. and AVP 10 units (Pitressin, Parke-Davis, Eastleigh, Hants) was

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injected i.m. immediately after the fentanyl. The preparation of the CRF and GHRH for human injection was undertaken as described previously [3]. Sodium chloride solution 150 mmol litre^{-1} was administered i.v. at a rate of 6 ml kg^{-1} h^{-1} during the operation and 2 ml kg^{-1} h^{-1} after operation. Blood transfusion was not required, as measured blood loss did not exceed 220 ml.

Further venous blood samples were obtained at the start of surgery (0 min) and 30, 60, 120 and 240 min after surgery commenced. Arterial pressure and heart rate were measured at the same time as the blood samples were collected. Serum concentrations of cortisol and GH were measured by sensitive and specific radioimmunoassays [2]. All samples were analysed in a single assay; the intra-assay coefficients of variation were 6% for cortisol and 8% for GH.

The results are presented as mean values (SEM). Statistical evaluation of the data was undertaken using either two-way or one-way analysis of variance as appropriate.

There were no significant differences between the two groups of patients with respect to age, body weight and duration of surgery (34.3 (1.3) yr, 60.5 (4.3) kg and 81 (5) min, respectively, in the fentanyl-only group and 32.1 (1.6) yr, 58.3 (2.2) kg and 87 (4) min, respectively, in the releasing factors group).

Serum concentration of cortisol increased slowly in those patients who received fentanyl alone, from 222 nmol litre^{-1} at the start of surgery to a peak value of 492 nmol litre^{-1} after 120 min ($P < 0.05$) (fig. 1). In contrast, in the releasing factors group, cortisol increased significantly from 235 nmol litre^{-1} at the start of surgery to 562 nmol litre^{-1} after only 30 min ($P < 0.01$) and reached 736 nmol litre^{-1} after 120 min ($P < 0.001$). Serum concentrations of cortisol were significantly greater in the releasing factors group compared with the fentanyl-only group after 30, 60, 120 and 240 min ($P < 0.01$).

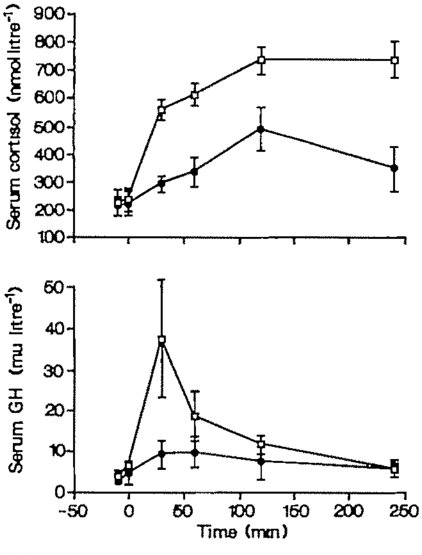

FIG. 1. Mean (SEM) serum concentrations of cortisol and growth hormone (GH) in patients receiving fentanyl only (●) and fentanyl + hypothalamic releasing factors (□).

In the fentanyl-only group, serum GH increased from 4.8 mu. litre^{-1} at the start of surgery to 9.8 mu. litre^{-1} after 60 min, before declining to 5.9 mu. litre^{-1} after 240 min (fig. 1) (ns). The administration of releasing factors resulted in a massive increase in serum GH, from 6.3 mu. litre^{-1} at the start of surgery to 37.4 mu. litre^{-1} after only 30 min ($P < 0.01$) and 18.8 mu. litre^{-1} after 60 min ($P < 0.05$). Serum concentrations of GH were significantly greater in the releasing factors group compared with the fentanyl-only group after 30 min ($P < 0.05$).

COMMENT

The results show that the inhibitory effects of fentanyl 15 µg kg^{-1} on the pituitary–adrenal response to pelvic surgery may be overcome by the concomitant administration of CRF, GHRH and AVP. This indicates that the primary site of action of fentanyl during surgery is hypothalamic, either directly or indirectly, rather than pituitary.

Our findings are contrary to the conclusions drawn in a few previous studies examining the site of action of morphine in man [4, 5], in which it was concluded that morphine acted predominantly at the pituitary. It is important to note that both these studies examined the effects of morphine on basal and CRF-stimulated ACTH secretion in resting man. The present study is, we believe, the first to examine the site of action of an opioid given to inhibit stress-induced pituitary secretion in man. This important physiological difference, the stress of surgery compared with rest, may explain partly the discrepancy in the results. The dose of fentanyl used in this study, 15 µg kg^{-1}, is approximately equivalent to morphine 1.5 mg kg^{-1}. This equivalent dose of morphine is considerably greater than the 0.14 mg kg^{-1} s.c. used by Rittmaster and colleagues [5] and the 30 mg orally given by Allolio and colleagues [4]. We cannot exclude the possibility that other doses of fentanyl may act at sites additional or alternative to the hypothalamus.

Nevertheless, our observation of a possible hypothalamic site of action of fentanyl is in keeping with other clinical data. It has been shown on many occasions that a given dose of opioid inhibits the secretion of several pituitary hormones simultaneously (ACTH, GH and AVP), in addition to suppressing sympathetic nervous system activity [1]. This strongly suggests a hypothalamic site, as the separate and distinct stimulatory and inhibitory mechanisms for each peptide militate against a single distal site of action.

We chose to administer AVP together with CRF and GHRH because it has been shown that the addition of AVP increases further the cortisol and GH responses to the hypothalamic factors [3]. The cortisol response found in patients who received fentanyl together with the releasing factors was almost identical to that obtained previously in patients undergoing the same surgery without an opioid [6]. It is tempting to infer that the cortisol changes observed in patients not receiving an opioid represented the maximal ACTH response, and that CRF and AVP were the major releasing factors involved in stimulating ACTH secretion during surgery. In contrast, the GH values found after GHRH and AVP were far greater than those noted without an opioid [6], indicating that the GH response to surgery did not represent maximal secretion.

In conclusion, fentanyl 15 $\mu g\ kg^{-1}$ attenuated the pituitary–adrenal hormonal response to surgery in man by an effect mediated via the hypothalamus.

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ANAESTHETIC MANAGEMENT OF SYSTEMIC MASTOCYTOSIS

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SUMMARY

Systemic mastocytosis is an uncommon disorder of mast cell proliferation in connective tissues. Mast cell degranulation may occur on exposure to various stimuli and drugs. The release of histamine, heparin and vasoactive substances such as prostaglandin D_2 may cause severe hypotension and other anaphylactoid manifestations. Anaesthetic management should include perioperative stabilization of mast cells and avoidance of the use of histamine-releasing drugs. Intradermal skin testing is useful in predicting the sensitivity to drugs that may be used during anaesthesia. We present a patient with systemic mastocytosis who underwent uneventful cholecystectomy.

KEY WORDS
Allergy · intradermal testing. Complications: mastocytosis.

Mastocytosis is an uncommon disorder (1–4 in 10000) of mast cell proliferation, which occurs in both cutaneous (urticaria pigmentosa) and, in about 10% of cases, systemic forms. As the mast cell is a connective tissue cell, the systemic disorder may involve all organs except the central nervous system. Mast cell degranulation occurs in response to a variety of non-immune triggers, including physical or psychological stimuli, in addition to exposure to many nutrients and drugs. The release of the preformed granule-associated mediators such as histamine, heparin and many enzymes (chymases, hydrolases, tryptases) and the generation of leucotrienes, prostaglandin (PG) D_2 and platelet-activating factor may produce significant systemic effects [1]. Cardiovascular collapse, bronchospasm and death during anaesthesia in patients with systemic mastocytosis have been documented [2]. A patient with systemic mastocytosis was anaesthetized for cholecystectomy at our institution.

CASE HISTORY

A 65-year-old, 63-kg female with systemic mastocytosis was admitted to the surgical department of the University Hospital, Ghent for elective cholecystectomy. From the age of 19 yr the patient had experienced recurrent flushes and urticarial weals, pruritus, dizziness and headaches after consumption of alcohol and exposure to heat. A diagnosis of "urticaria pigmentosa" had been confirmed by skin biopsy 15 yr previously. She had suffered a major syncopal episode and dyspnoea during dental treatment. Severe flushing and dyspnoea had occurred after injection of the local anaesthetic during an earlier attempt to aspirate bone marrow. None of the attacks required her admittance to hospital. Her past medical history included haemorrhoidectomy under regional anaesthesia, appendicectomy and lens implantation under general anaesthesia. Each postoperative period was accompanied by abdominal cramps, diarrhoea, flushing and vomiting.

In January 1989 the patient was admitted to the University Hospital, Ghent with complaints of diarrhoea, abdominal pain in the right upper quadrant and hot flushes associated with dyspnoea. Physical examination showed a moderately obese woman in no acute distress. Her skin had a coalescent brownish-red macular appearance on the trunk, upper and lower extremities. Darier's sign (dermographism) was positive, with a weal and flare after scratching the skin. Abdominal examination showed deep tenderness in the right upper quadrant. The liver edge was felt 8 cm below the costal margin.

ECG and chest x-ray examinations were normal, while x-rays of the thoracic and lumbar spine showed osteoporosis. Abdominal x-ray showed

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calcification in the gall bladder and cholelithiasis was confirmed by ultrasonography. Laboratory results, including coagulation studies, thyroid function, plasma concentrations of catecholamine and urinanalysis, were normal. Colonoscopy was negative, but the biopsies contained many mast cells. Gastroscopy showed signs of gastritis. A bone marrow biopsy showed an increased number of mast cells (4% of marrow cells) with a spindle shape.

The diagnosis of systemic mastocytosis was confirmed by the history, bone marrow biopsy and response to antihistamine therapy with normalization of defaecation. Terfenadine and famotidine, H_1- and H_2-receptor blockers and enteric coated aspirin were commenced. The patient was scheduled to undergo cholecystectomy.

Premedication comprised famotidine 20 mg, terfenadine 60 mg, aspirin 1 g and lorazepam 2.5 mg, orally. Standard monitoring, including invasive measurement of arterial pressure and bladder catheterization was commenced and skin tests of drugs thought necessary for anaesthesia were performed. The drugs tested included: normal saline control, etomidate, vecuronium, atropine, cefuroxime, adrenaline, hydrocortisone, meglumine–amidotrizate (the water-soluble iodinated radiographic contrast medium for use during the cholangiogram) and fentanyl. After the disappearance of the reactive flare, an erythematous weal persisted at the sites of injection of etomidate and hydrocortisone. Propofol was tested, without a reaction. Cefuroxime 1.5 mg was administered i.v. as antibiotic prophylaxis.

Anaesthesia was induced with propofol, vecuronium and fentanyl. After tracheal and gastric intubation, anaesthesia was maintained with isoflurane and nitrous oxide with an $F\text{I}_{O_2}$ of 0.5 and supplemented with fentanyl and vecuronium. Ventilation of the lungs was adjusted to achieve mild hypocapnia ($P\text{E}'_{CO_2}$ 4 kPa). Cholecystectomy was carried out through an upper median incision. The gall bladder had a calcified appearance and was found to be filled with multiple small stones. An intraoperative cholangiogram was performed and showed a normal common bile duct, free of stones. The patient withstood the operative procedure well. There were no episodes of flushing, hypotension, bronchospasm or other untoward events during operation.

I.v. administration of H_1- and H_2-receptor blocking agents and aspirin was continued in the postoperative period. Postoperative pain relief was achieved with i.v. piritramide, after prior skin testing. Postoperative recovery was satisfactory, complicated only by an episode of diarrhoea and mental disorientation on the third night after operation. The patient was discharged on the 11th day after operation, with continuation of aspirin, terfenadine and famotidine therapy, and has remained well.

DISCUSSION

The most common sites involved in systemic mastocytosis are skin, bone, gastrointestinal tract, liver, spleen and lymph nodes (table I). The anaesthetic management of systemic mastocytosis has previously been associated with a high perioperative complication rate. Parris, Scott and Smith reported cardiovascular collapse or bronchospasm requiring adrenaline infusion in five of 42 patients (12%) [2].

Complete assessment of the degree of systemic involvement of the disease must be made before operation. Laboratory evaluation of mast cell degranulation involves measurements of plasma and urinary concentrations of histamine [3], urinary PG D_2 and its metabolite PG D_2M [4] and plasma concentrations of tryptase. Urinary concentrations of histamine correlate better with tissue concentrations of histamine than plasma concentrations of histamine and the complexity of the measurement of PG D_2 restricts its wider clinical application. An immunoassay of tryptase as a marker of the release of mast cell granules may be useful as a measure of perioperative activation of mast cells [5].

The preoperative use of H_1- and H_2-receptor blocking agents is generally recommended, although others have doubted their value [6]. The effect of histamine on capillary permeability appears to be mediated via H_1-receptors, but the vasodilator action involves both H_1- and H_2-receptors, so that both must be blocked to have any certain prophylactic effect.

The implication of PG D_2 as a mediator of the hypotensive episodes has led to the use of prostaglandin synthetase inhibitors, such as aspirin. Oral administration of disodium cromoglycate 4 × 100 mg has been shown to produce an improvement in cutaneous and gastrointestinal symptoms. As cromoglycate is poorly absorbed by oral administration, inhalation is preferable. The elimination half-life of cromoglycate is about 80 min, so its use as a premedicant drug is limited.

TABLE I. *Manifestations of systemic mastocytosis*

	Signs	Symptoms
Cutaneous	Dermographism Flushing Urticarial weals Reddish-brown papulae	Pruritus
Cardiovascular	Tachycardia Hypotension Syncope	Palpitations
Gastrointestinal	Hepatosplenomegaly Predeliction for Gastric ulcer Malabsorption (rare) Portal hypertension (rare)	Nausea Vomiting Diarrhoea Abdominal pain
Bone	Osteoporosis Pathological fractures	Bone pain
Neurological		Headache
Respiratory	Wheezing	Rhinorrhoea Dyspnoea
Haematological	Anaemia Leucopenia Thrombocytopenia (rare) Decreased clotting factors Leukaemia (rare)	Coagulopathies

Ketotifen also prevents mast cell degranulation and may prove to be of value in perioperative treatment.

Stress can precipitate a reaction, so sedative premedication is important and benzodiazepines are appropriate. Extremes of temperature should be avoided and pressure on, trauma to or rubbing the skin must be restricted to a minimum. Temperature, ECG and arterial pressure should be monitored continuously and the possibility of sudden haemodynamic instability some time after a drug has been injected must be borne in mind [7]. The drug of choice for correction of hypotension is adrenaline 5–8 $\mu g\ kg^{-1}$ i.v., followed by a continuous infusion of 5–10 $\mu g\ kg^{-1}\ min^{-1}$. Doses of 1–3 $mg\ kg^{-1}$ i.v. may be used to manage acute exacerbations of systemic mastocytosis as part of the conventional management of anaphylactoid reactions. Although heparin is released by mast cell degranulation, there are no reports of haemorrhagic complications during anaesthesia, probably because of phagocytosis of the endogenously released heparin. There may, however, be other reasons for a haemorrhagic diathesis, such as hepatic fibrosis, malabsorption of vitamin K secondary to intestinal lesions and thrombocytopenia caused by bone marrow suppression.

The choice of anaesthetic technique depends on the type of surgery. Some authors suggest that, in the absence of a coagulopathy, regional anaesthesia with an amide-linked local anaesthetic is preferable. However, a severe urticarial reaction has been described following i.v. regional anaesthesia with lignocaine [8]. Parris, Scott and Smith also experienced more complications with regional anaesthesia and commonly, as in our patient, intolerance to lignocaine [2]. As inhalation anaesthetics tend to inhibit the degranulation of mast cells, general anaesthesia using halothane, enflurane or isoflurane may be preferable.

Intradermal skin testing has been advocated, to enable prediction of reactions to drugs. False negative results are possible, and the chance of a false positive result increases with increasing concentration of drug. A standard procedure using 0.01–0.02 ml of a dilute solution (10^{-4}–10^{-6}) to raise a 1–2 mm weal is advocated in the diagnosis of drug-related acute anaphylactoid reactions [9]. As, in the case of systemic mastocytosis, non-specific histamine release occurs and most patients are receiving antihistamines and disodium cromoglycate at the time of preoperative skin testing, we advocate greater concentrations such as 10^{-2} or 10^{-3}. The criteria for a positive reaction should be strictly defined as a weal appearing within 10 min, lasting at least 30 min and at least 10 mm in diameter for an injected volume of 0.1 ml.

Intradermal testing was useful in the selection of propofol as the induction agent in the present patient, thus confirming the absence of histamine release after induction doses of the emulsion formulation of propofol [10, 11].

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ANAESTHETIC MANAGEMENT OF MYOCARDIAL INFARCTION IN A PARTURIENT

L. S. AGLIO AND M. D. JOHNSON

SUMMARY

Myocardial infarction is encountered rarely during pregnancy, but when it occurs the event is life-threatening to both mother and fetus. Data on maternal and fetal outcome are limited, but overall maternal mortality approaches 35%, and 40% of deaths occur during the third trimester. We present a case of myocardial infarction occurring at 38 weeks gestation, and discuss the anaesthetic management of the problems encountered during labour and delivery.

KEY WORDS

Anaesthesia: obstetric. Complications: myocardial infarction

Myocardial infarction (MI) is a rare complication of pregnancy. However, when it occurs the event is life-threatening to both mother and fetus. We present a case of MI occurring at 38 weeks gestation.

CASE REPORT

An obese, 26 yr-old gravida 2, para 1 woman at 38 weeks gestation noted the acute onset of precordial chest pain radiating to her left arm accompanied by sweating, nausea and vomiting. She presented to a local hospital approximately 3 h after the onset of pain. On admission, she denied shortness of breath, palpitations, abdominal pain, vaginal bleeding, premature contractions or rupture of membranes. ECG demonstrated anterolateral ST elevation associated with right bundle branch block and left posterior hemiblock. A diagnosis of acute MI was confirmed, with a maximum serum concentration of creatine kinase of 638 iu litre^{-1}. She was treated with i.v. nitroglycerin and oral diltiazem. Chest x-ray revealed no signs of congestive heart failure. Her condition remained stable and she was transferred to the Brigham and Women's Hospital Coronary Care Unit 48 h after the onset of symptoms.

The patient was a cigarette smoker and had a 6-month history of hypertension controlled with a low sodium diet. Her past obstetric history included spontaneous normal vaginal delivery at 42 week gestation after a 6-h labour. The current pregnancy had been uncomplicated and the estimated gestational age was believed to be accurate.

On admission the heart rate was 120 beat min^{-1}, arterial pressure 115/80 mm Hg, ventilatory frequency 20 b.p.m. and oral temperature 36.5 °C; body weight was 105 kg, height 155 cm. Jugular venous pressure and heart sounds were normal. Auscultation of the chest revealed diffuse expiratory rhonchi. The abdomen was soft and non-tender, with a gravid uterus. Repeat chest x-ray showed no signs of congestive heart failure and ECG was unchanged.

In anticipation of possible premature delivery, a pulmonary artery catheter was inserted. Right atrial pressure initially was 8 mm Hg and pulmonary capillary wedge pressure (PCWP) 12 mm Hg. Two-dimensional echocardiography revealed extensive anteroapical and anteroseptal akinesia, with moderate impairment of left ventricular function, traces of mitral and tricuspid insufficiency and a minor pericardial effusion. The obstetric ultrasound examination was consistent with a single fetus of approximately 32 weeks gestation in vertex position with a heart rate of 140 beat min^{-1}. Estimated fetal weight was 3580 g.

Because of the uncertain aetiology of the MI, initial management included oral diltiazem and

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i.v. heparin (because of the possibility of a procoagulant state). She had no further chest pain, in spite of persistent tachycardia. On the 3rd day in hospital, the patient developed proteinuria accompanied by impaired liver function tests suggestive of pre-eclampsia. The 24-h urine protein output was 961 mg in 2175 ml and creatinine clearance was 154 ml min^{-1}. Proteinuria resolved spontaneously and liver function tests returned to normal 3 days later.

During the hospital stay, signs of labour were absent. Twelve days after diagnosis of the acute MI (at 39 and 5/7 weeks), pelvic examination revealed a soft cervix at 2 cm dilatation with 80 % effacement. The probability of spontaneous labour in the succeeding few days was believed to be approximately 50 % and it was decided to attempt to induce labour. Heparin was discontinued (activated clotting time 128 s (normal = 80–120 s)) and the patient was transferred to an operating room while receiving 40 % oxygen by face mask. Monitoring comprised intra-arterial pressure, pulmonary artery pressure, finger pulse oximetry and ECG.

An extradural catheter was sited via a 17-gauge Weiss needle inserted by a midline approach at the L3–4 interspace using the hanging drop technique. An initial test dose of 2 ml of 2 % plain lignocaine was injected and the catheter was directed 2 cm cephalad. The patient was placed supine with a wedge under the right hip. When bilateral sensory analgesia had been demonstrated by pinprick, 3-ml aliquots of 2 % plain lignocaine were given. A total of 18 ml was given to obtain a level of anaesthesia to T6.

An i.v. infusion of nitroglycerin was commenced at 0.5 $\mu g\ kg^{-1}\ h^{-1}$ and ECG leads II and V5 were monitored continuously. Vaginal amniotomy was performed and i.v. oxytocin given by infusion to initiate labour. An extradural injection of fentanyl 50 μg in normal saline 10 ml was given at induction. Anaesthesia was maintained with a continuous infusion of 2 % lignocaine with fentanyl 2 μg/ml of lignocaine, at a rate of 10 ml h^{-1}.

After 5 h, labour had progressed to 4 cm dilatation. PCWP was 10 mm Hg at induction and, despite judicious administration of nitroglycerin i.v., had increased to 27 mm Hg after 8 h. Extradural anaesthesia was extended to T4 and Caesarean delivery was performed with a vertical skin incision and a vertical uterine incision. A male infant was delivered, weighing 3.15 kg with Apgar scores of 8 and 9, umbilical vein pH of 7.34 and umbilical artery pH of 7.30. Estimated blood loss was 700 ml. The patient was transferred directly to the Coronary Care Unit, where her condition remained stable. Haemodynamic monitoring was continued for 48 h and the extradural catheter was left in place for administration of fentanyl.

Eighteen days after MI, radionuclide ventriculography revealed a left ventricular ejection fraction of 40 %. Cardiac catheterization revealed a filling defect compatible with thrombus in the proximal left anterior descending artery, with 70 % stenosis. Ventriculography demonstrated anterior wall hypokinesis, apical dyskinesis and intraventricular mural thrombus. The patient was treated initially with heparin i.v. followed by oral coumarin for 6 month, and discharged 21 days postpartum receiving oral atenolol 50 mg daily.

DISCUSSION

Myocardial infarction during pregnancy, described first in 1922 [1] is rare, with an incidence estimated at 1 in 10000 pregnancies [2, 3]. To date, 82 cases have been reported [1–11]. The greatest incidence is in the third trimester in women older than 35 yr. Hankins and colleagues [12] emphasized that most maternal deaths occur either at the time of infarction, with an undeliverable child, or within 2 weeks of MI. Postpartum MI is associated with a high mortality, tending to occur in young primigravidae with pre-eclampsia [5].

Among the 82 reports, 52 patients delivered vaginally with a maternal mortality rate of 12 %, while 14 underwent Caesarean delivery with a mortality of 21 %, although the two groups were not strictly comparable. In general, fetal outcome correlated with maternal outcome. Of 75 fetuses, 23 died, and 65 % of these deaths occurred at the same time as maternal death.

Approximately 30 % of parturients had coronary artery morphology defined either by angiography or at postmortem, as follows: significant coronary atherosclerosis was found in approximately 40 %; definite coronary thrombus with "normal" coronary arteries was present in 30 %; probable coronary thrombus (angiographic evidence of total occlusion of a coronary vessel but with otherwise normal vessels) was diagnosed in 10–15 %; coronary aneurysm/dissection appeared in 10 %, and normal coronary arteries were found in approximately 10 %.

It has been suggested that coronary artery spasm in pregnancy may result from a transiently ischaemic chorion [13], as the human chorion contains 160 times more renin than maternal plasma [14, 15]. Formation of intracoronary thrombi, as a result of the potentially procoagulant state of pregnancy, may play a role [15, 16]. In addition, pregnant women who smoke are at increased risk of thrombus formation because of enhanced platelet aggregation [17]. Abnormalities of the coagulant and fibrinolytic systems which increase throughout pregnancy may contribute [15, 16].

In pregnancy numerous cardiovascular changes occur. Diaphragmatic elevation causes leftward deviation of the heart. An innocent grade I–II systolic murmur may be heard as a result of increased blood flow and vasodilatation. The ECG may show reversible ST, T and Q-wave changes. These normal findings must be differentiated from those indicating heart disease.

Cardiac output increases 15% during the latent phase of labour, 30% during the active phase, and 45% during the expulsive stage, in comparison with pre-labour values [18]. This increase in cardiac output is a result of increase in both heart rate and stroke volume [19, 20]. Each uterine contraction increases cardiac output by an additional 10–25% [19]. The greatest increase occurs immediately after delivery, when the cardiac output is, on average, 80% above pre-labour values [20]. This is attributed to autotransfusion associated with uterine contraction.

Choice of anaesthesia and method of delivery in a parturient with acute MI are controversial. Cohen reviewed the advantages and disadvantages of Caesarean *vs* vaginal delivery, with no convincing support for either [21]. Advantages of elective Caesarean delivery include ability to control the time of delivery, avoiding an unpredictable, stressful labour (table I). While vaginal delivery eliminates the stress of surgery, prolonged labour itself is stressful.

Hankins and colleagues advocated vaginal delivery [12], neglecting, however, to define the differences in patient populations between Caesarean and vaginal delivery: those undergoing Caesarean deliveries were at greatest risk, which would account for a poorer outcome. In the case reported here, Caesarean delivery was required after failed induction of labour and a prolonged course, resulting in an increase in PCWP. The increase in PCWP was presumed to reflect deteriorating left ventricular function. There was no change in the strength of uterine contractions and i.v. fluid volume was kept to a minimum.

No single method of anaesthesia is exclusively indicated. From experience in this department, we prefer extradural anaesthesia, and data from reported cases support this approach. Laughlin and associates used a modified Cleland two-catheter extradural technique [22]. During the first stage of labour, pain was controlled effectively by repeated injections of bupivacaine through the upper catheter and, for the second stage, lignocaine was injected through the lower catheter.

TABLE I. *Advantages and disadvantages of different modes of delivery of cardiac parturients. (Modified from [21] and [22])*

	Advantages	Disadvantages
Caesarean section (elective)	Eliminates the stress and unpredictability of labour. Time of delivery can be planned. Control of cardiopulmonary status.	Surgical stress. Increased cardiorespiratory and metabolic demands. Potential for increased blood loss. Postoperative infection.
Vaginal delivery (with extradural)	Stress of surgery eliminated. Less potential for blood loss. Less chance of postoperative infection. Early ambulation. Pain relief. Haemodynamic stability.	Prolonged labour causes stress. Unpredictable nature of delivery.

After delivery, the parturient should undergo cardiovascular evaluation to provide diagnostic and prognostic information, thereby aiding further management. This should include two-dimensional echocardiography and radionuclide ventriculography to assess left ventricular function. Holter monitoring and exercise tolerance testing should be performed. With this information, recommendations can be made for subsequent management and future pregnancies.

Among the cases reported during a pregnancy subsequent to that when MI occurred, there were no maternal deaths [23]. The only fetal death occurred at 22 weeks, as a result of an incompetent cervix. However, the data should be evaluated cautiously, as the numbers are small and the details often are not available. A previous MI, although not an absolute contraindication to future pregnancy, carries undoubted risk.

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COMPARISON OF TWO VENTILATORS USED WITH THE T-PIECE IN PAEDIATRIC ANAESTHESIA

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SUMMARY

The Nuffield 200 ventilator was compared with a new valveless ventilator (CW 200) in 20 children undergoing general anaesthesia for paediatric surgery. The new ventilator incorporates design features which overcome the main disadvantages of the Nuffield 200 and make it an inherently safer machine. At identical ventilator settings it produced a significantly greater tidal volume with a reduction in end-tidal carbon dioxide partial pressure. This may have advantages in avoiding pulmonary barotrauma in children.

KEY WORDS

Anaesthesia: paediatric Equipment: ventilators, T-piece.

Relatively few ventilators are convenient for use with the T-piece in paediatric anaesthesia. T-Piece occluders suffer from the drawback that the ventilatory fresh gas flow (FGF) is used not only to provide anaesthesia and oxygenation, but also to inflate the lungs. This makes these ventilators relatively inflexible in use, limits the age range over which they are practicable and requires FGF rates considerably in excess of those needed to maintain normocapnia.

Various modifications of adult ventilators have been described for use with the T-piece, the most recent of which uses a fixed orifice leak built into the patient valve of the Nuffield 200 ventilator [1]. This is a more versatile machine which works well in practice. However, it does have serious theoretical disadvantages, some of which make it potentially dangerous in clinical use. The purpose of this paper is to compare the performance of the recently described valveless all-purpose ventilator [2, 3] with that of the Nuffield 200 ventilator with the Newton valve modification and to evaluate both in a group of children during general anaesthesia.

MATERIAL AND METHODS

Clinical evaluation

The study, which was approved by the Hospital Ethics Committee, was performed in 20 children aged 4 months to 8 yr (mean age 2.9 (SD 2.3) yr) and who weighed between 5.8 and 26.3 kg (mean weight 13.1 (5.5) kg), receiving general anaesthesia for a variety of surgical conditions (table I).

Anaesthesia was induced with cyclopropane in oxygen or i.v. thiopentone and maintained with 70 % nitrous oxide in oxygen supplemented with either 0.5–1 % halothane or i.v. fentanyl. Tracheal intubation was facilitated by suxamethonium 1–2 mg kg^{-1}, after which neuromuscular block was maintained with atracurium (initial bolus dose of 0.5 mg kg^{-1}, followed by an infusion of 8 µg kg^{-1} min^{-1}) monitored by peripheral nerve stimulation.

TABLE I. *Details of the 20 patients*

Age (yr) (mean (SD))	2.9 (2.3)
Range	0.25–8.0
Weight (kg) (mean (SD))	13.1 (5.5)
Sex (M/F)	15/5
Type of operation	
Urological	7
Plastic	7
Abdominal	5
Dental	1

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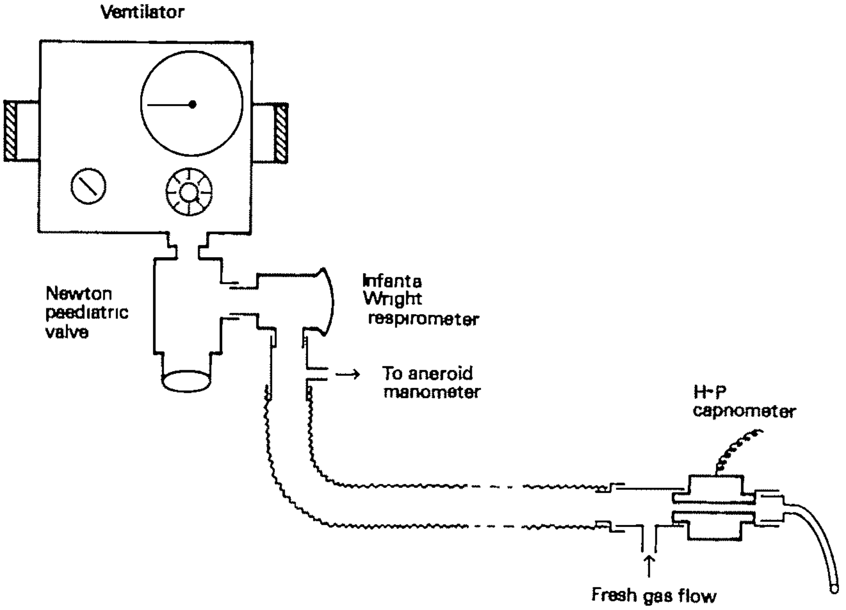

FIG. 1. Diagram of apparatus used in the study, shown with the N 200 ventilator.

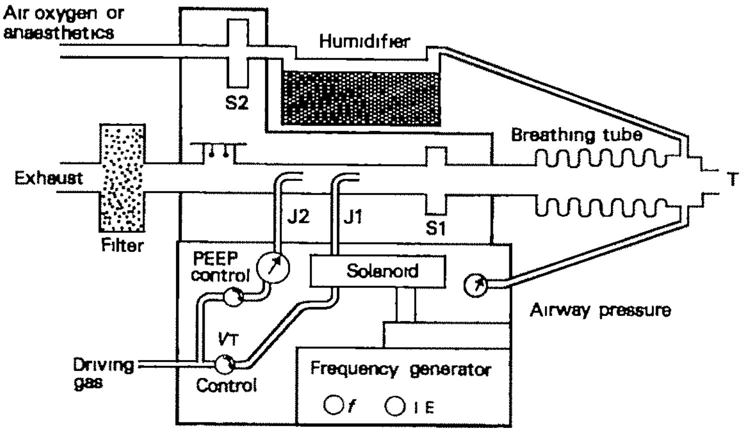

FIG. 2. Diagrammatic representation of CW 200 ventilator. J1 = Driving jet; J2 = positive end-expiratory pressure (PEEP) jet; T = tracheal tube. The ventilating frequency and I:E ratio are controlled by an electronic pulse generator operating a solenoid valve. The fresh gas flow is displayed continuously by a flow sensor, S2, (Magtrack) which is provided with an alarm for a minimum set flow. The expired tidal and minute volumes are measured by using another similar flow sensor, S1, and taking the difference in reading between S1 and S2 during the expiratory phase.

Mechanical ventilation was commenced using either the Nuffield 200 ventilator with a Newton valve (N 200) (fig. 1) or the all-purpose valveless ventilator (CW 200) (fig. 2), attached to the expiratory limb of a modified T-piece. The choice of initial ventilator for each patient was made by random selection. FGF was set according to weight (less than 10 kg: 3 litre min^{-1}; 10–15 kg: 4.5 litre min^{-1}; more than 15 kg: 6 litre min^{-1}) using flowmeters which were calibrated against those of known accuracy. Tidal volume ($V\text{T}$) was adjusted to ensure adequate chest movement, with an inspiratory:expiratory (I:E) ratio of 1:2. The ventilatory frequency (f) was set at 14–30 b.p.m. according to the age of the child. The inspired oxygen concentration ($F\text{I}_{\text{O}_2}$) was monitored with a fuel cell, peripheral oxygen saturation (Sa_{O_2}) with a pulse oximeter, and end-tidal carbon dioxide partial pressure ($P\text{E}'_{CO_2}$) with a Hewlett–Packard infra-red capnometer (model 4721DA with digital and paper readout), calibrated before each study. The capnometer cuvette was placed in the apparatus deadspace and the paediatric cuvette (deadspace 2 ml) was used in children weighing less than 10 kg. Airway pressure within the breathing system was measured using an aneroid manometer (0–7 kPa); its accuracy was checked against a mercury column manometer.

Systemic arterial pressure (SAP) was measured every 3 min with an automated cuff (Dinamap) and the ECG and beat-by-beat heart rate (HR) recorded. A precordial stethoscope was applied routinely. Train-of-four responses to peripheral nerve stimulation (either the ulnar or tibial nerves) were maintained at less than 25 % throughout the period of study. Measurements of *f* and $P\text{E}'_{CO_2}$ from the capnometer, Sa_{O_2}, SAP, HR and peak inflation pressure (PIP) were made at 5-min intervals for 15 min after $P\text{E}'_{CO_2}$ had stabilized. The volume of gas leaving the ventilator during inspiration was measured also, using a Wright Infanta respirometer, which records V_T accurately between 15 and 200 ml [4], placed in the distal limb of the T-piece as close as possible to the ventilator.

After the 15-min measurement period a change was made to the alternate ventilator, which was adjusted to the same *f*, PIP and I:E ratio as the first machine. The measurements described above were then repeated at 5-min intervals for a further 15 min. In two subjects the surgical procedure was of sufficient duration to allow the patient to be returned to the first ventilator and for the initial measurements to be repeated.

Laboratory evaluation

The pressure, flow and volume wave forms developed by each ventilator were recorded in the laboratory under identical conditions. Each ventilator in turn was connected by a standard Jackson–Rees modification of Ayre's T-piece to a model lung with a compliance set at either 10 or 30 ml kPa^{-1} and a resistance set at either 10 or 20 kPa litre^{-1} s. The peak inflating pressure was set as close as possible to 2 kPa with *f* at 20 b.p.m. and an I:E ratio of 1:2. Pressure changes at the junction between the model lung and the T-piece were measured with a Validyne MP 45 (±5 kPa) pressure transducer, and air flow was measured using a Fleisch No. 0 pneumotachograph connected to a Validyne MP 45 (±0.2 kPa) differential pressure transducer. The flow signal was integrated electronically to give volume. Time-based pressure, flow and volume signals were stored on a Compaq Deskpro 110 computer and displayed on an Epson FX 850 printer.

RESULTS

Clinical evaluation

In all children the CW 200 produced a greater V_T for a given airway pressure than the N 200, the smallest increase being 17 % and the largest being 173 % in individual patients, with an overall 19 % mean increase of 46 (19.6) ml, from 93 ml to 139 ml (table II) ($P < 0.001$).

TABLE II. *Tidal volumes produced by the CW 200 and N 200 ventilators at identical frequencies and peak airway pressures (I:E ratio 1:2)*

Patient No.	Tidal volume (ml)		
	CW 200	N 200	CW 200−N 200
1	55	33	22
2	170	115	55
3	110	90	20
4	305	220	85
5	55	33	22
6	140	120	20
7	280	200	80
8	200	150	50
9	175	125	50
10	180	110	70
11	160	120	40
12	155	120	35
13	100	50	50
14	125	53	72
15	85	40	45
16	60	23	37
17	60	22	38
18	85	50	35
19	105	50	55
20	170	140	30
Mean (SD)	139	93	46 (19.6)
Range			22–85

In all patients, $P\text{E}'_{CO_2}$ was less during ventilation with the CW 200 than with the N 200, with differences ranging from 0.14 kPa (3 %) to 0.93 kPa (19 %), and an overall mean difference of 0.55 kPa (11.5 %) ($P < 0.001$), (table III).

No significant changes in HR, SAP or Sa_{O_2} were seen during the study period in any patient.

TABLE III. *End-tidal carbon dioxide partial pressures ($P_{E'_{CO_2}}$) produced by the CW 200 and N 200 ventilators at identical frequencies and peak airway pressures (I:E ratio 1:2)*

Patient No.	$P_{E'_{CO_2}}$ (kPa) CW 200	N 200	N 200 − CW 200
1	5.32	5.85	0.53
2	4.39	5.32	0.93
3	4.12	4.26	0.14
4	3.19	3.72	0.53
5	3.72	4.12	0.4
6	4.52	4.92	0.4
7	4.12	5.05	0.93
8	3.99	4.26	0.27
9	3.59	3.99	0.4
10	3.86	4.79	0.93
11	4.26	4.79	0.53
12	4.52	4.79	0.27
13	3.86	4.79	0.93
14	4.26	4.92	0.66
15	3.59	4.39	0.80
16	5.19	5.59	0.40
17	5.59	5.85	0.26
18	3.46	3.72	0.26
19	5.05	5.85	0.80
20	3.33	3.86	0.53
Mean (SD)	4.19	4.74	0.55 (0.26)
Range			0.14–0.93

Laboratory evaluation

Whilst the pressure wave produced by the N 200 was similar to that of a pressure generating ventilator, the pressure wave produced by the CW 200 was almost square (fig. 3). The flow and volume waves changed as expected for pressure generating ventilators when the compliance and resistance of the model lung were changed.

DISCUSSION

Both the CW 200 and the N 200 ventilators are easy to use with the paediatric T-piece, as each can be attached to the expiratory limb instead of the manual inflation bag, acting very much as an "educated hand". As the driving gas used to inflate the lungs is independent of the ventilatory FGF, controlled rebreathing techniques may be used in infants and young children with FGF as low as 1000 + 200 ml kg^{-1}, without causing hypercapnia [5] and with a reduction in heat and water vapour loss. The ability to control arterial partial pressure of carbon dioxide (Pa_{CO_2}) by adjusting the FGF independently of the degree of lung inflation may be of benefit to patients in low

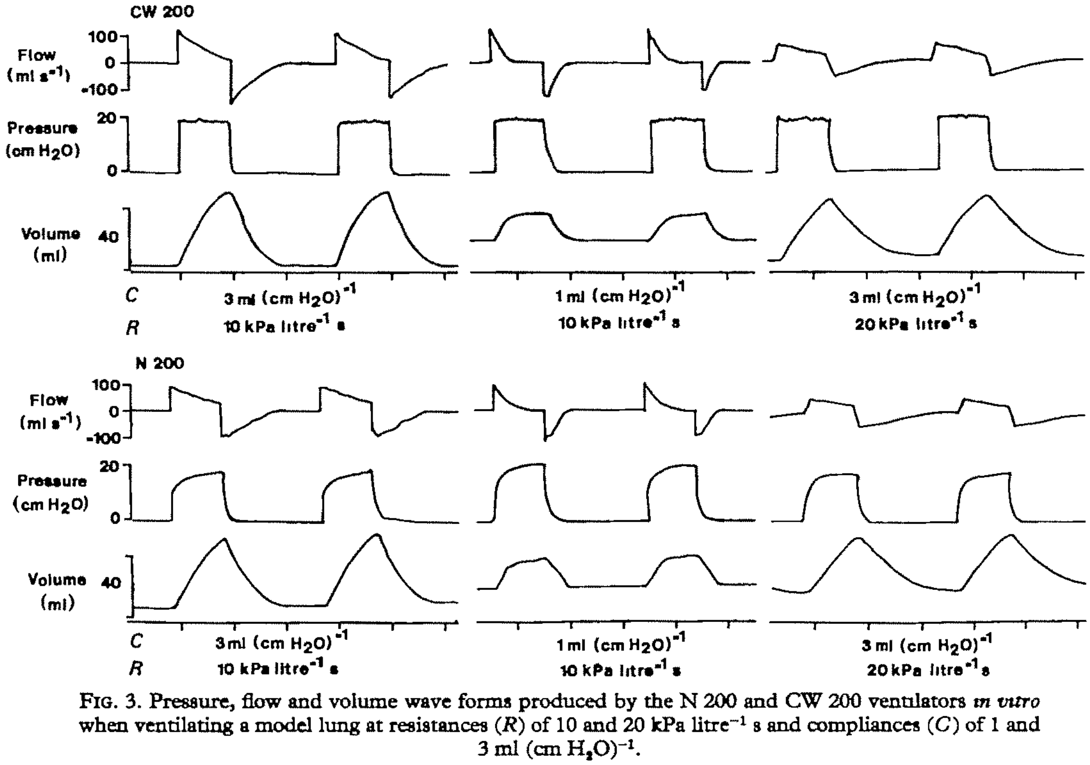

FIG. 3. Pressure, flow and volume wave forms produced by the N 200 and CW 200 ventilators *in vitro* when ventilating a model lung at resistances (R) of 10 and 20 kPa litre^{-1} s and compliances (C) of 1 and 3 ml (cm H_2O)$^{-1}$.

output cardiac failure and in the avoidance of bronchopulmonary dysplasia [6, 7].

Although the Nuffield 200 ventilator has proved satisfactory in practice, there are several disadvantages to the fixed orifice leak principle, which make it potentially very dangerous. Newton, Hillman and Varley [1] demonstrated that the modified Nuffield ventilator behaves as a pressure generator, and our *in vitro* measurements (fig. 3) confirmed this. As with any pressure generator, reduction in compliance or increase in resistance at the patient end of the system leads to a reduction in ventilation. This underventilation may not be apparent by visual observation of the pressure monitor, and airways obstruction may not always be detected by the pressure alarm, as in small children the PIP is determined largely by the size of the leak through the Newton valve. Volume alarms are difficult to fit because of the continuous flow of the FGF passing through the expiratory limb of the T-piece, in addition to the expired volume. It is also possible to have apparently satisfactory ventilation with good chest movement despite significant rebreathing if the FGF is inadequate. Finally, the modified valve is suitable only for children up to about 15 kg, with an unmodified valve being required for larger children. The repeated changing of the valve required if children above and below this weight are to undergo ventilation is time consuming and may eventually cause damage to the valve. It is sometimes impossible to avoid the application of a small amount (0.1–0.2 kPa) of positive end-expiratory pressure (PEEP), especially in older children.

Although the CW 200 has also been shown to have the characteristics of a pressure generator [2], again confirmed in this study (fig. 3), it incorporates design features which overcome the problems described above. It is suitable for use at all ages from birth to adult life, without modification. Expired volume is monitored by automatic subtraction of the ventilatory FGF flowing in expiration from the total expired volume, allowing tidal and minute volumes to be displayed continuously, with appropriate alarms, in addition to an FGF failure alarm. The expired volume signal could be used to provide feed-back information to the driving jet, which would enable the machine to deliver a servo-controlled volume. The PEEP is adjusted easily, and as it is a valveless ventilator it can be used for weaning children from ventilatory support through intermittent mandatory ventilation without the need for sensitive triggering devices, on to continuous positive airway pressure. If desired, the new ventilator can be used also at high frequencies of ventilation.

The results of this study show that, when compared with the N 200 in the same patient at identical settings, the CW 200 ventilator gave a significantly greater V_T for a given peak inflation pressure, with a consequently lesser $P_{E'_{CO_2}}$ in every patient. As volume and pressure were measured between the expiratory valve and the patient, this difference cannot be explained by the amount of gas passing through the fixed orifice leak of the N 200 ventilator. This was confirmed by the finding of a similar difference in older children, in whom the adult valve with no leak was used on the N 200 ventilator. Although the small amount of PEEP which is sometimes unavoidable with the N 200 may have been responsible for a slight reduction in tidal volume, the most likely explanation for these findings would appear to be the striking difference between the inspiratory pressure wave-forms produced by the two machines (fig. 3). A very important feature of the CW 200 is that V_T is generated by the driving jet and not by the ventilatory FGF, which can be kept constant. At ventilatory frequencies up to 80 b.p.m., the inflation pressure profile is virtually a square wave, which implies that the PIP is applied throughout the inspiratory time. This is in contrast to the ramp function of the pressure wave produced by the N 200, and to the "thumb" devices with which the PIP is not reached until the ventilatory FGF generates a preset pressure in the system. This makes the CW 200 a much more efficient machine, particularly when inspiratory time is short and pulmonary compliance low, and may have important implications for the avoidance of bronchopulmonary dysplasia in infants with respiratory distress syndrome [6, 7]. Clinical studies have already shown improved results in very low birthweight babies with severe respiratory disease [8]. In conventional thumb devices, in order to increase the V_T, FGF has to be greatly increased so that the preset pressure is reached earlier in the inspiratory phase, which in turn generates uncontrolled and possibly undesirable PEEP because of the resistance of the expiratory limb of the system.

This study has demonstrated that the CW 200 ventilator is not only a safer, more flexible ventilator than the N 200 for use with the paediatric T-piece, but that it is more efficient in terms of producing a significantly greater $V\mathrm{T}$ for a given peak inflation pressure under the conditions of the study. It is the first paediatric T-piece ventilator to provide an alarm responsive to $V\mathrm{T}$ in addition to the more conventional pressure alarms, and thus presents a major step forward in patient safety for ventilators used with the paediatric T-piece. Because there are no valves or other obstructions in the breathing duct, the patient can breathe freely at all times, allowing the provision of intermittent mandatory ventilation without complex systems for synchronization. PEEP can be applied deliberately as the frequency of ventilation is increased beyond the predicted time constant of the lungs.

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RAPIDITY AND ACCURACY OF TRACHEAL INTUBATION IN A MANNEQUIN: COMPARISON OF THE FIBREOPTIC WITH THE BULLARD LARYNGOSCOPE

A. DYSON, J. HARRIS AND K. BHATIA

SUMMARY

Successful tracheal intubation with the flexible fibreoptic bronchoscope requires a certain amount of skill which is acquired by practice. It has been suggested that the new Bullard laryngoscope may be mastered more easily. To determine if learning was superior with a flexible fibreoptic or the Bullard device, the ease of tracheal intubation with both devices was compared by first-year anaesthetic residents, using a mannequin modified to make intubation difficult. The Bullard laryngoscope was as easy to master as the flexible fibreoptic device, but passage of the tracheal tube took longer. Both devices require a similar amount of practice.

KEY WORDS

Intubation, tracheal. training, fibreoscopy. Equipment laryngoscope

Recognition and subsequent management of the difficult airway are complex problems for both trainee and teacher [1–3]. Studies have demonstrated advantages of flexible fibreoptic bronchoscopes over conventional laryngoscopes [4–6]. However, they require a significant time to prepare, may not be readily available, and require a significant amount of teaching and continued practice [1, 7].

The Bullard laryngoscope has been designed to circumvent some of these difficulties. It is a combination of an anatomically shaped rigid blade with a fibreoptic light source to aid direct visualization of the larynx and subsequent tracheal intubation. The adult version (fig. 1) may be prepared as rapidly as a conventional laryngoscope.

A recent study suggested that the device might be easier to master than the flexible fibreoptic laryngoscope, permit rapid visualization of the vocal cords and oral tracheal intubation, and offer the potential for a low risk of failed intubation [8].

The purpose of this study was to ascertain if the Bullard laryngoscope is easier for residents to master than "conventional" fibreoptic intubation.

METHODS

Twenty residents of less than 1 year of anaesthetic experience were invited to pass a tracheal tube into a mannequin which had been adjusted so that tracheal intubation was as difficult as possible. Only the epiglottis was *just* visible (to a senior anaesthetist) using a Macintosh blade. This corresponds to grade III of Cormack and Lehane's classification as modified by Samsoon and Young [9, 10]. Residents were asked to attempt tracheal intubation using three methods:

(1) Fibreoptic oral tracheal intubation, without any assisting devices except jaw lift provided, if requested, by a helper.

(2) Bullard laryngoscope using an oral tracheal tube introduced over a stylet.

(3) Bullard laryngoscope using the forceps port to introduce a flexible metallic wire into the trachea, followed by removal of the blade and passage of the oral tracheal tube over the wire through the larynx.

A standardized description and demonstration of each method was given to each resident, followed by one practice attempt.

Each resident performed each technique 10

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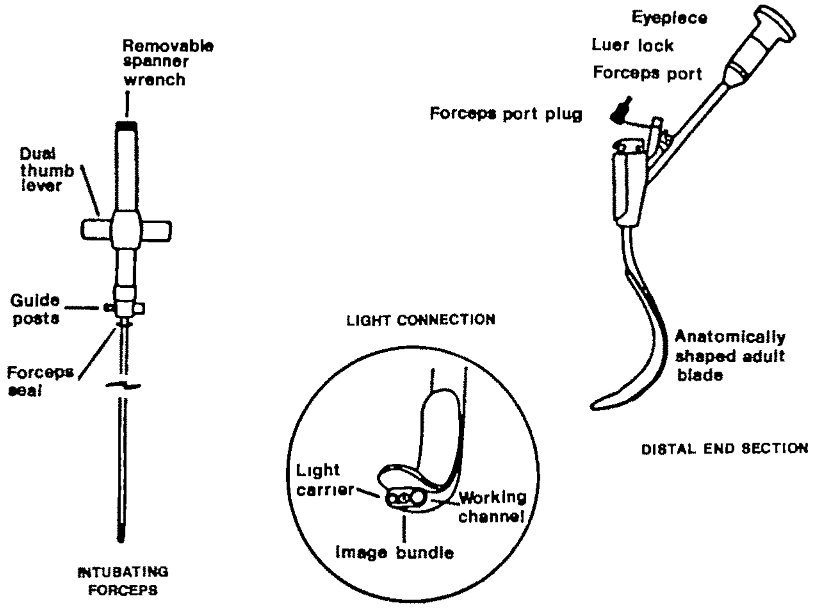

FIG. 1. The Bullard laryngoscope.

TABLE I. *Mean* (SD) *time for tracheal intubation and degree of difficulty.* *P < *0.05 compared with first five attempts;* †P < *0.05 compared with fibreoptic;* ***P < *0.001 compared with other techniques*

	Time for intubation (s)		
	Fibreoptic	Bullard + stylet	Bullard + wire
All 10 intubations	15.0 (3.9)*** ($n = 200$)	22.4 (7.2) ($n = 200$)	28.5 (5.8) ($n = 200$)
First five intubations	19.0 (4.3) ($n = 100$)	27.3 (6.4) ($n = 100$)	31.7 (6.9) ($n = 100$)
Second five intubations	12.1 (4.3)* ($n = 100$)	19.1 (6.3)* ($n = 100$)	25.0 (5.6)* ($n = 100$)
Degree of difficulty (1–10)	2.1 (0.9)	2.9 (1.4)†	2.1 (1.5)

times in succession. The order in which the methods were performed was determined from a random number table. Thus a total of 600 tracheal intubations were attempted. The time from the blade passing the lips of the mannequin to successful placement of the tube was recorded in each case. At the end of each sequence the residents were asked to attach a degree of difficulty to the method, using a scale from 1 = extremely easy to 10 = impossible. The number of failed tracheal intubations was also recorded, defined as one that required more than 60 s or which resulted in oesophageal intubation.

Results were analysed using Wilcoxon's rank sum test for non-parametric data.

RESULTS

Tracheal intubation was fastest with the flexible fibreoptic device (mean 15 s) ($P < 0.001$) and this technique was also easier to use than the Bullard with the stylet (degree of difficulty 2.1 *cf.* 2.9 ($P < 0.05$)) (table I). Although using the Bullard blade with the wire took longer, it was judged to be as easy as the fibreoptic method.

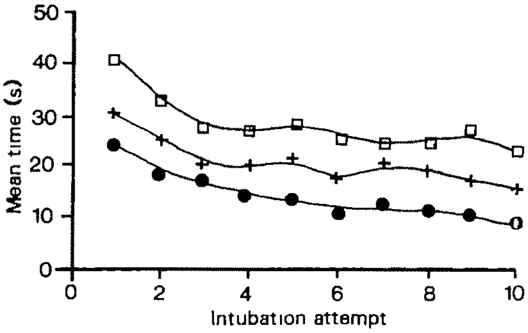

FIG. 2. Changes in time for tracheal intubation with practice using three different techniques. □ = Bullard + wire; + = Bullard + stylet; ● = fibreoptic device.

Use of the Bullard and wire was associated with the fewest failed intubations, although this was not significant. In all there were two failed intubations with method (1), six with method (2) and none with method (3).

Improvement with practice was apparent with all these methods (fig. 2). The differences between the first five and the second five tracheal intubations were significant for all three methods ($P < 0.05$).

DISCUSSION

The results suggest that no single technique for the management of difficult intubation is learned easily, but any may be improved by practice. In particular, the Bullard laryngoscope was not easier to use than the flexible fibreoptic device with either of the methods used. The Bullard was found also to be less reliable when used with a stylet than with the flexible metallic wire, but the latter method took significantly longer. Although the fibreoptic device proved faster to use, this advantage may be outweighed by the time it takes to prepare the apparatus for use, as the Bullard can be prepared in the same time as an ordinary laryngoscope.

In clinical practice, we have found that the Bullard laryngoscope provides an excellent view of the vocal cords, but passage of a tracheal tube around it is often difficult. The use of the "railroading" technique provides a partial solution, but takes longer. If the reliability of this method can be substantiated in clinical practice it may be useful in situations where no appropriately trained anaesthetist is available.

The Bullard laryngoscope is rugged and less susceptible to damage from misuse. Breakage of this instrument should be rare, in contrast with the flexible device, which is also time consuming to repair. The Bullard has a slight advantage over flexible instruments in terms of cost. The high cost of flexible instruments has been cited as a major reason for the current paucity of anaesthetists in the U.K. familiar with their use [1]. One substantial disadvantage compared with flexible fibreoptic devices is the necessity for the patient to be able to open the mouth before the Bullard can be used.

In conclusion, we have been unable to demonstrate that the Bullard laryngoscope is easier to learn than the flexible device. However, it may provide a reliable alternative to flexible fibreoptic devices.

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All authors have certified that, where appropriate, studies have been conducted with the approval of the relevant Human Ethics Committee or Animal Experimental Review Committee.

CLEARANCE OF ATRACURIUM, LAUDANOSINE AND MONOQUATERNARY ALCOHOL BY HAEMOFILTRATION IN THE CRITICALLY ILL PATIENT

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A constant infusion of atracurium is now used regularly in the intensive therapy unit in the critically ill patient with renal and respiratory failure in whom it is impossible to establish adequate artificial ventilation (IPPV) using sedatives and opioids alone [1]. However, concern has been expressed that, although atracurium is cleared rapidly from the body, cumulation of breakdown products, the toxic concentrations of which are uncertain in man, may occur if renal or liver function is impaired [2].

The use of mechanically pumped veno–venous haemofiltration (VVHF) is particularly useful in these patients, especially if they show cardiovascular instability. It allows easily controllable removal of extracellular fluid in addition to correction of abnormal concentrations of urea and electrolytes, even when the patient is inotrope dependent. Many drugs will also be removed by this technique. We therefore compared the clearance of atracurium and its metabolites, laudanosine and monoquaternary alcohol (MQA) from the plasma with the notional clearance through the haemofiltrate.

We studied five patients undergoing IPPV and continuous VVHF using a Gambro AK10 system with FH66 fibre haemofilters. The patients were receiving continuous infusions of morphine 2–10 mg h^{-1}, midazolam 2–10 mg h^{-1} and atracurium 0.3–0.8 mg kg^{-1} h^{-1}. The blood flow through the filter was maintained at 125 ml min^{-1} and the outflow from the filter was restricted to give an average haemofiltrate flow of 19 ml min^{-1} (27.3 litre day^{-1}). A total of 33 samples of arterial blood and haemofiltrate were taken simultaneously from the five patients. Samples were assayed for atracurium, laudanosine and MQA by an HPLC technique [1].

The mean (SEM) clearances for atracurium, laudanosine and MQA in the plasma at steady state and through the haemofiltrate are given in table I. The clearance achieved by VVHF was derived from the Sieving coefficient (S):

$$Cl = S \times \text{HF flow [3]}$$

VVHF was found not to be an effective method of removing atracurium or its metabolites from the body. Its use does not, therefore, necessitate adjustment to the rate of infusion of atracurium.

TABLE I. *Mean* (SEM) *clearances for atracurium, laudanosine and MQA*

	Atracurium	Laudanosine	MQA
Plasma Cl^{ss}	6.5	4.5	2.3
(ml kg^{-1} min^{-1})	(0.97)	(0.8)	(0.38)
VVHF Cl	0.11	0.09	0.19
(ml kg^{-1} min^{-1})	(0.03)	(0.02)	(0.01)

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IS THE ACTION OF SUXAMETHONIUM IN CHILDREN AGE-DEPENDENT?

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We investigated possible age-dependent sensitivity to suxamethonium in 150 children (ASA I) during induction of anaesthesia with halothane (maximal inspiratory concentration 1.5%). Following Ethics Committee approval, they were studied in five age groups ($n = 30$) (1–11 months, 12–23 months, 24–35 months, 36–71 months and older than 71 months) and allocated randomly to receive suxamethonium 0.25, 0.5 or 1.0 mg/kg body weight. Potency and duration of action of suxamethonium were measured electromyographically (supramaximal train-of-four stimulation of the ulnar nerve every 20 s) using a Datex NMT device. Onset time, maximal suppression of the response to stimulation (*D*max) and total duration of recovery to 90% were evaluated.

TABLE II. *Dmax (mean values and range) (% of baseline)*

Dose of sux. (mg kg^{-1})	Age (months)				
	1–11	12–23	24–35	36–71	> 71
0.25	40 (10–85)	26 (11–91)	23 (8–71)	35 (7–61)	45 (7–90)
0.5	79 (58–100)	80 (31–95)	78 (36–100)	84 (65–100)	92 (55–100)
1.0	99 (97–100)	99 (95–100)	98 (90–100)	100 (97–100)	99 (96–100)

Statistical analysis was by Mann–Whitney *U* test.

In all groups examined, *D*max increased with dose of suxamethonium (table II). Significant differences between age groups were observed only with suxamethonium 0.25 mg kg^{-1}, infants and children older than 71 months having a significantly greater *D*max than children of younger age groups. In all age groups, suxamethonium 1 mg kg^{-1} caused 90–100% suppression of the response to stimulation and provided good conditions for intubation.

The duration of action of suxamethonium 1 mg kg^{-1} was significantly longer in children aged 36–71 months and children older than 71 months (means 4.9 min and 6.1 min, respectively) than that in younger children (average about 3.5 min). There were no significant differences between age groups with smaller doses.

Thus, even with large population samples, it was not possible to demonstrate age-related differences in sensitivity of children to suxamethonium. In most children from each age group, suxamethonium 1 mg kg^{-1} with halothane produced 100% suppression of the response to stimulation, and good conditions for intubation. While use of larger doses may prolong the duration of action, no additional improvement in intubating conditions is likely to be achieved.

RELATIONSHIP OF PLASMA CONCENTRATION OF ATRACURIUM TO RESPONSE USING THE TRAIN-OF-FOUR RATIO

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Ten healthy patients were anaesthetized with thiopentone 3–5 mg kg^{-1} and 66% nitrous oxide in oxygen, supplemented with fentanyl 200–500 µg and midazolam 3–10 mg, and the electromyographic response of adductor pollicis to train-of-four (TOF) stimuli recorded every 12.5 s using a Medelec MS6. Atracurium 0.25 mg kg^{-1} was then administered by constant infusion over 10 min and blood samples taken for assay of plasma atracurium as described previously in a study of the relationship of the first twitch of the TOF A′/A to plasma concentration of atracurium [1]. In the present study an attempt was made to fit the same standard dynamic model [2] to the depression of the TOF ratio, D′/A′ and the plasma atracurium profile. Residual errors were of an order of magnitude greater than those obtained on fitting the data set for A′/A. It can be shown graphically that the large residual error represents a systematic lack of fit of the model to the data which, in addition, could not be improved using the more recently described threshold model [3].

An attempt was made, therefore, to fit the data set D′/A to both the standard and the threshold models. The fit was associated with residual errors comparable to those obtained for the data set A′/A [3]. The threshold model was again preferred in every case. The variable values for $C_P{}^{ss}{}_{50}$ and k_{e0} were little affected by the choice of model and showed a high linear correlation with the values of these variables for A′/A in the same patient ($P < 0.001$ in both instances; Student's *t* test on the correlation coefficient). As in the previous study [3], however, the value of gamma was markedly reduced in the threshold model (table III).

TABLE III. *Mean* (SD) *variable values for the standard and threshold models for D′/A*

	Standard model		Threshold model	
$C_P{}^{ss}{}_{50}$ (ng ml^{-1})	370	(71)	368	(71)
Gamma	4.35	(0.74)	2.79	(0.32)
k_{e0} (min^{-1})	0.103	(0.019)	0.105	(0.019)
Threshold (ng ml^{-1})	—		152	(38)

Unlike A′/A and D′/A, the TOF ratio D′/A′ is not related to plasma atracurium concentration within the context of a simple pharmacodynamic model.

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NITROUS OXIDE POTENTIATES SUXAMETHONIUM BLOCK IN MAN

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The ED$_{90}$ of suxamethonium at the adductor pollicis has been reported to be 0.27 mg kg^{-1} [1] and 0.51 mg kg^{-1} [2]. The drug was given shortly after induction of anaesthesia in the second study, but 5–10 min after induction of anaesthesia in the first study, in which nitrous oxide was administered. We tested whether duration of anaesthesia, nitrous oxide, or both, potentiated suxamethonium block.

Sixty adult subjects (ASA I and II) were allocated randomly to receive suxamethonium 0.3 mg kg^{-1} after induction of anaesthesia with thiopentone 5–7 mg kg^{-1}. In group I, suxamethonium was given 1 min after induction. In group II, thiopentone alone was used to maintain anaesthesia and suxamethonium was given after induction. In group III, 70% inspired nitrous oxide in oxygen was given via a mask and suxamethonium was administered 6 min after induction. In all subjects, supramaximal train-of-four stimulation was delivered to the ulnar nerve every 12 s, starting 30 s before suxamethonium was administered. The force of contraction of the adductor pollicis muscle was recorded.

Student's t test with Bonferroni correction for multiple comparisons was applied, and $P < 0.05$ was considered statistically significant.

Prolonging exposure to thiopentone did not affect maximal block, which was (mean (SEM)) 61 (6)% and 54 (8)% in groups I and II, respectively. However, the addition of nitrous oxide (group III) potentiated the block (80 (6)%; $P < 0.02$ compared with group II). Time to maximum block did not differ significantly between groups (131 (7) s, 139 (10) s and 130 (7) s in groups I, II and III, respectively).

The potentiation of block was unrelated to the duration of anaesthesia *per se*. Previous discrepancies [1, 2] in the estimates of the potency of suxamethonium can be explained by the presence [1] or absence [2] of nitrous oxide. Large doses of suxamethonium are required usually after induction of anaesthesia, partly because nitrous oxide has not then been administered.

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PLASMA PROTEIN BINDING OF ALFENTANIL: EFFECTS OF AGE, PREGNANCY AND CANCER

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Alfentanil is highly bound in plasma to proteins, particularly alpha-1 acid glycoprotein (AAG) [1], and many factors may influence the plasma concentration of AAG [2]. We investigated the effects of age, pregnancy and cancer on plasma binding of alfentanil.

The study was approved by the local Ethics Committee. None of the patients was receiving medication known to affect the plasma concentration of AAG. Subjects included nine pregnant women (23–36 yr) and their newborn (39–41 weeks gestation), eight infants (3–11 months), nine children (3–10 yr), nine patients with cancer (26–60 yr) and 17 adults (26–40 yr). Neonatal blood samples were drawn from the umbilical cord immediately after birth; in other subjects, venous blood samples were drawn from a vein during the preoperative period. Protein binding was determined by equilibrium dialysis at 37 °C of plasma 1 ml against buffer 1 ml (pH 7.4) containing tritiated alfentanil 500 ng (specific activity 23.1 Ci mmol^{-1}). Concentrations of alfentanil in plasma and buffer were determined by measurement of radioactivity.

TABLE IV. *Plasma concentrations of unbound alfentanil and AAG (mean (SD))*

Group	*n*	Alfentanil (% free)	AAG (g litre^{-1})
Newborn	9	37.1 (7.2)	0.27 (0.05)
Infants	8	14.0 (5.5)	0.51 (0.20)
Children	9	7.5 (0.9)	0.83 (0.20)
Pregnant women	9	17.5 (2.0)	0.61 (0.17)
Adults	17	7.9 (1.6)	0.75 (0.21)
Cancer patients	9	4.2 (1.2)	2.02 (0.59)

After equilibrium, the free fraction was calculated as the concentration of alfentanil in the buffer divided by the concentration in the plasma.

Differences between groups were tested by analysis of variance and Newman–Keuls test. The correlation between plasma concentration of AAG and free fraction of alfentanil was tested by the significance of the r value determined by least-squares linear regression. $P < 0.05$ was considered significant.

The free fraction of alfentanil was greater in the newborn than in the other age groups ($P < 0.01$) (table IV). The free fractions in infants and in pregnant women were significantly greater than in children ($P < 0.01$) or adults ($P < 0.01$). In adult cancer patients, the free fraction of alfentanil was smaller than in the control adult group ($P < 0.01$). The free fraction of alfentanil was inversely correlated with the plasma concentration of AAG ($r = 0.57$; $P < 0.001$).

These results are similar to those obtained in previous studies with other basic drugs such as propranolol or lignocaine. Changes in plasma concentration of AAG could be an important factor in determining the free fraction of alfentanil.

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FURTHER DEVELOPMENT OF THE MORPHINE HYDROGEL SUPPOSITORY

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Previous work has shown that the morphine hydrogel suppository (MHS) is capable of maintaining plasma morphine concentrations for periods of up to 12 h [1]. The present study evaluated a preproduction preparation in volunteers. The study was approved by the Ethics Committee and all subjects gave informed consent after being screened for haematological and biochemical abnormalities and drugs of abuse.

A 100-mg MHS with an *in vitro* release rate of approximately 10 mg h^{-1} was administered to five male volunteers (A–E). Blood was sampled at frequent intervals for 24 h and urine collected for two 12-h periods and analysed for morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) by HPLC. The MHS was removed after 12 h and analysed for residual content of morphine. Side effects were measured by verbal rating and linear analogue scales.

The MHS had a mean content of morphine of 103 mg. Complete retrieval at 12 h was possible in subjects A, B, D and E and the doses given were 58.9, 53.6, 44 and 62.8 mg, respectively.

Plasma concentrations of morphine, M6G and M3G increased to approximately steady mean values of 15, 50 and 350 ng ml^{-1}, respectively, after 2 h and were maintained to 12 h, when they declined rapidly in four subjects. Subject D had consistently lesser values throughout and the MHS was found to be poorly hydrated at its base as a result of incomplete insertion. Subject C had considerably greater plasma concentrations of morphine, M6G and M3G (8.2, 25.3 and 185 ng ml^{-1}, respectively) at 24 h. Complete removal had been impossible in this subject and approximately 50% was retained.

Mild sedation was noted by all subjects (two dizziness, three nausea, one vomited). All side effects were mild and did not prevent normal activities.

The study confirmed that MHS is capable of attaining and maintaining analgesic plasma concentrations of morphine for up to 12 h. The mean plasma concentrations were comparable to those attained after similar doses of oral morphine given over the same time period. This suggests that the rectal bioavailability of morphine is comparable to that of the oral route. Plasma concentrations of M3G and M6G were also comparable, implying similar metabolic patterns. Approximately 50% of the contained morphine was released in 12 h from the MHS. The presence of near analgesic plasma concentrations at 24 h in one subject who retained portions of the MHS suggests that these suppositories may be capable of administering morphine for 24 h.

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PULSE OXIMETRY AND THE ARTERIAL TO END-TIDAL $P\text{CO}_2$ DIFFERENCE IN CYANOTIC CHILDREN

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From the shunt equation, it is possible to derive the relationship between the respiratory quotient R and end-capillary and arterial contents (Cc′, Ca) of oxygen and carbon dioxide [1]:

$$R = (C\text{a}_{\text{CO}_2} - C\text{c}'_{\text{CO}_2})/(C\text{c}'_{\text{O}_2} - C\text{a}_{\text{O}_2})$$

Thus, for any degree of cyanosis resulting from right–left shunting, there is an obligatory arterial–end-capillary carbon dioxide content difference. Assuming that pulmonary end-capillary $P\text{CO}_2$ is equivalent to end-tidal $P\text{CO}_2$ ($P\text{E}'_{\text{CO}_2}$), then:

$$P\text{a}_{\text{CO}_2} - P\text{E}'_{\text{CO}_2} = R\cdot k_1\cdot(100 - S\text{a}_{\text{O}_2}\%)/k_2$$

where k_1 and k_2 are conversion factors that transform $S\text{a}_{\text{O}_2}$ and $P\text{CO}_2$ to blood-gas content. The former can be derived for different haemoglobin (Hb) concentrations, by assuming an oxygen combining factor for Hb of 1.34 ml g^{-1}, and k_2 can be estimated from diagrams produced by Nunn [2]. The term k_2 is dependent both on the absolute value of $P\text{CO}_2$ and on oxygenation—the Haldane effect. Assuming an R value of 0.8, $R\cdot k_1/k_2$ can be estimated to vary between 0.03 and 0.04 when $P\text{a}_{\text{CO}_2}$ is 4.0. The greatest values for $R\cdot k_1/k_2$ should be obtained in polycythaemic, cyanotic children.

Sixty-one observations were made in 32 cyanotic children undergoing elective cardiac surgery. Most (48) were made before surgery or immediately after sternal opening. The rest were made after bypass. The lungs of all children were ventilated by a Servo 900 C ventilator during anaesthesia with 50% nitrous oxide in oxygen supplemented by halothane or fentanyl. $P\text{E}'_{\text{CO}_2}$ was measured with a Siemens-Elema 930 CO_2 analyser. ($P\text{a}_{\text{CO}_2} - P\text{E}'_{\text{CO}_2}$) was corrected for temperature and for alinearity and other analyser errors [3]. In addition, $S\text{a}_{\text{O}_2}$ values of 100% were assumed in 12 children with normal pulmonary circulation studied before pulse oximeters were available. Their mean $P\text{a}_{\text{O}_2}$ value was 30 kPa (min. 24 kPa). A Nellcor pulse oximeter was used for most observations ($n = 31$), Novametrix and Radiometer for the rest. The regression equation obtained was.

$$(P\text{a}_{\text{CO}_2} - P\text{E}'_{\text{CO}_2}) = 4.72 - 0.0469 \times S\text{a}_{\text{O}_2}\%,\ r = -0.86$$

In the $S\text{a}_{\text{O}_2}$ range 60–100% it was:

$$P\text{a}_{\text{CO}_2} - P\text{E}'_{\text{CO}_2} = 3.99 - 0.0387 \times S\text{a}_{\text{O}_2},\ r = -0.84$$

Thus, at saturations of 60–100%, ($P\text{a}_{\text{CO}_2} - P\text{E}'_{\text{CO}_2}$) increased by about 0.4 kPa for every 10% reduction in $S\text{a}_{\text{O}_2}$, which agrees well with the prediction for an R value of 0.8. At lower saturations, the increase in ($P\text{a}_{\text{CO}_2} - P\text{E}'_{\text{CO}_2}$) was somewhat greater, possibly consistent with the appearance of secondary effects of right–left shunting—that is, pulmonary hypoperfusion. This may develop if cardiac output cannot be increased enough to compensate for the intracardiac shunt. Secondary effects are therefore most likely to occur at low saturations.

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CHAOS IN VENTILATORY TIMING IN ANAESTHETIZED MAN?

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We are not surprised when complicated mathematical models in physiology and pharmacology fail to predict behaviour, but we expect simple models to behave predictably. This may be naive.

May described an apparently simple model of insect populations:

$$p_{n+1} = C\cdot p_n\cdot 1 - p_n$$

where $0 < p < 1$ and is the population in year n or year $n+1$, and C is a scaling parameter. The behaviour of this equation was important in the development of the study of

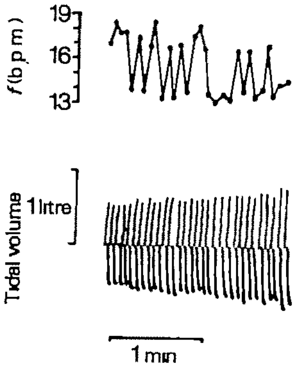

FIG. 1. Carbon dioxide rebreathing in a patient anaesthetized with propofol [3]. Above: instantaneous frequency. Below: ventilatory volume by pneumotachography, inspiration upwards (record retouched).

chaos [1]. For a process showing chaotic behaviour, small variations in input can cause large variations in output and the process is no longer predictable. It can be difficult to distinguish chaos from randomness, particularly in stochastic processes such as occur in biology. Between order and chaos, processes show the phenomenon of "period doubling": an initially steady output begins oscillating between two values, each of these values also bifurcate, and this continues until chaos supervenes.

The patterns of breathing of 32 patients were recorded in two studies, of the effects of propofol [2] and propofol and alfentanil [3]. Five of these patients showed evidence of bimodality of ventilatory frequency when anaesthetized. This bimodality was entirely of expiratory time, and was independent of tidal volume (fig. 1) (see also figures 2 and 3, ref [3]). No explanation of the phenomenon was offered in the first study [2]; in the second [3], its occurrence was offered as support for the existence of a multi-oscillator in the respiratory centre.

This phenomenon could be similar to the period doubling seen in other systems during the development of chaos. Anyone studying patterns of breathing should be aware of descriptions of chaos, because only then will they recognize and report it and enable us to define the conditions under which chaos is likely to arise.

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BREATH BY BREATH GAS EXCHANGE MEASUREMENT DURING GENERAL ANAESTHESIA

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The use of breath by breath measurement of gas exchange in anaesthesia has been limited by the need to correct for the wide range of gas composition changes encountered with anaesthetic gases. Furthermore, the absence of nitrogen from air in the inspired gases prevents the assumption of nitrogen equilibrium at the mouth being used to correct for changes in lung gas stores from breath to breath.

A system has been developed that will measure the gas exchange breath by breath of up to eight gases, using a single pneumotachograph, a mass spectrometer and a microcomputer. Correction of inspired and expired volumes for changes in gas composition was made after the time delay between flow information and concentration information had been eliminated by the microcomputer program. Correction for lung gas stores can be performed using nitrogen or argon as the equilibrium gas. Inspired argon concentration (0.93% v/v) may be maintained during general anaesthesia and the correction implemented.

Results for use of the system for air breathing volunteers and patients breathing nitrous oxide in oxygen during i.v anaesthesia have been obtained and compared with the results obtained using Douglas Bag measurements. For air breathing volunteers, the mean error for $V\mathrm{CO_2}$ was 0.8 ml breath^{-1} (3.21%) and for $V\mathrm{O_2}$ 1.2 ml breath^{-1} (5.1%). Mean variation breath to breath was not changed significantly by the application of lung gas stores correction for $V\mathrm{CO_2}$, but improved from 12.19 ml breath^{-1} to 8.67 ml breath^{-1} for nitrogen and 10.47 ml breath^{-1} for argon. For patients under anaesthesia, error of measurement was better than 0.61 ml breath^{-1} (5.6%) for spontaneously ventilating patients and better than 1.54 ml breath^{-1} (10.9%) during IPPV. For spontaneously ventilating patients with argon correction for lung gas stores, mean variation between breaths was improved from 2.0 ml to 0.7 ml for $V\mathrm{CO_2}$, 4.45 ml to 3.59 ml for $V\mathrm{O_2}$ and 8.1 ml to 5.35 ml for $V\mathrm{N_2O}$. For IPPV, the comparable figures were $V\mathrm{CO_2}$ 1.38 to 0.97 ml, $V\mathrm{O_2}$ 3.68 to 1.44 ml and $V\mathrm{N_2O}$ 5.66 to 6.62 ml.

The accuracy of the method during general anaesthesia is very similar to that of the same method in the hands of other workers with air breathing subjects. Application of the lung gas stores correction leads to reduced between-breath variation of measurement during anaesthesia. The experiments have illustrated the need for a true breath by breath gas exchange calibrator for the testing of similar systems, and that the breath by breath measurements may not be the method of choice for simple RQ or mean gas exchange measurements over minutes.

CONTINUOUS MEASUREMENT OF FRC DURING GENERAL ANAESTHESIA

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The use of the lung gas stores correction in the measurement of gas exchange breath by breath requires the use of an estimated value of lung volume. By examining the changes in the value of the end-tidal equilibrium gas, it has been proposed that an estimate of lung volume could be made [1]. Two methods have been proposed for this. Effective Lung Volume (ELV) is arrived at using a regression technique over an epoch of several breaths. It is that estimate of lung volume that minimizes the measured fluctuations breath by breath in either $\dot{V}co_2$ or $\dot{V}o_2$ over that epoch [2]. Average Lung Volume (ALV) has been proposed as that value of lung volume that would minimize the fluctuations breath by breath in lung volume as detected by the lung gas stores correction. Both should correlate with the volume of gas in lung engaged in gas exchange, and hence with FRC.

To test this, a modified version of the breath by breath gas exchange measurement system reported earlier was prepared that produced running estimates of ELV and ALV. The starting estimate FRC required by the measurement system was made using nomograms of height and age. The modifications were tested for correct functioning using a sample set of data from a single volunteer.

The output from the system was then compared with values of FRC measured for 10 supine, air breathing volunteers. The ELV or ALV measurements for the volunteers were first established over 10 to 20 breaths. A measurement of FRC using a Gould–Godart Pulmonet Spirometer was then made immediately using argon dilution. After a time allowed for elimination of argon from the volunteer, the measurements were repeated with the volunteers seated.

The experiment failed to give correlatable ELV results.

Measurements of ALV from argon data gave $r = 0.54$ ($P = 0.05$) and those from nitrogen data gave $r = 0.73$ ($P = 0.01$). This gave a confidence limit to any interpolation from the data of 2.48 litre and 1.43 litre, respectively.

Examination of the errors associated with the calculation of ELV suggest that it may be adversely affected by the lower tidal volumes and irregular breathing patterns of the volunteers.

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VENTILATORY RESPONSES TO SEVOFLURANE AND HALOTHANE IN THE RAT

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Sevoflurane, like halothane, is pleasant smelling and non-irritating to the tracheobronchial tree. With a low blood-gas solubility of 0.69, it is a good induction and maintenance anaesthetic agent. We have compared the effects on tidal volume, frequency and total ventilation of equipotent (1–2 MAC) concentrations of sevoflurane and halothane in five adult Wistar rats.

Each rat (300–350 g) was anaesthetized with each agent in oxygen in random order with a 2-week interval. The rat was intubated with a 16-gauge Venflon tube and sealed into a plethysmograph (Buxco). Calibration of the plethysmograph was made repeatedly by the injection and withdrawal of 2 ml of air and leaks excluded. Inspired concentrations (stepwise) of 2, 3, 4 and 5% sevoflurane or 1, 1.5, 2 and 2.5% halothane and then in reverse were administered for 10 and 15 min, respectively, and measured with a Normac anaesthetic agent monitor. End-tidal concentrations, which could not be measured in spontaneously breathing rats with rapid ventilatory frequency, were estimated from a computer program, NARKUP [1] designed for man, by supplying the program with exposure times which were six times longer than the actual experimental exposures [2] (six is the cube root of the ratio of the body masses of man and rat). Body temperature was maintained by an automatic heat source. Concentrations were expressed in MAC units by dividing the calculated end-tidal concentrations of sevoflurane and halothane by their respective MAC values as determined in our Department.

Table V shows, for each concentration of halothane and sevoflurane in the five rats, total ventilation, tidal volume and ven-

TABLE V. *Ventilatory variables (mean (SD)) at each concentration of halothane (H) and sevoflurane (S) in five rats*

MAC units		$\dot{V}$ (ml min^{-1})		V_T (ml)		f (b.p.m.)	
H	S	H	S	H	S	H	S
0.96	0.90	170 (9.6)	159 (22.6)	2.30 (0.32)	2.84 (0.55)	75 (8.7)	57 (6.4)
1.25	1.27	135 (6.8)	115 (9.2)	2.12 (0.28)	2.71 (0.42)	64 (7.0)	43 (6.8)
1.5	1.65	111 (9.0)	93 (11.8)	1.92 (0.24)	2.54 (0 42)	59 (8.1)	37 (6.1)
1.91	2.04	84 (16.4)	75 (12.0)	1 65 (0.18)	2.31 (0.44)	50 (7.4)	33 (6.8)
		ns		$P < 0.01$		$P < 0.01$	

tilatory frequency. The effects of the two agents were compared by parallel line regression of each ventilatory variable on log concentration. This showed that the depression of total ventilation was similar for the two agents, but tidal volume was depressed more for halothane than for sevoflurane ($P < 0.05$), whereas frequency was depressed more for sevoflurane than for halothane ($P < 0.01$).

Thus, in equipotent concentrations, sevoflurane and halothane depress total ventilation approximately equally. However, the mechanisms are different. As sevoflurane depresses frequency rather than tidal volume, the effect on alveolar ventilation will be less than that with halothane and this may compensate, or more than compensate, for the non-significant difference in total ventilation.

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EFFICIENCY OF A NEW ENCLOSED AFFERENT RESERVOIR BREATHING SYSTEM DURING CONTROLLED VENTILATION

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A new anaesthetic breathing system has been developed which incorporates an enclosed afferent reservoir (EAR). The circuit contains, in the inspiratory limb, a rising bellows assembly enclosed within a rigid container which is pressurized by an Ohmeda 7800 series ventilator during inspiration. The efficiency of this system was determined by calculating the fractional utilization of fresh gas (f) during anaesthesia with controlled ventilation [1].

The study was approved by the District Ethics Committee. Ten patients (ASA II–III) were anaesthetized with propofol followed by vecuronium 0.1 mg kg^{-1} to facilitate tracheal intubation. Anaesthesia was maintained with 66% nitrous oxide in oxygen and 1–2% v/v isoflurane. Initial settings of minute volume ($\dot{V}$E) and fresh gas flow (FGF) were guided by laboratory test results. $\dot{V}$E:FGF ratio was varied from 0.4 to 2.5. Twenty minutes was allowed at each setting for stabilization before measurement of $F\bar{E}_{CO_2}$, FE'_{CO_2} and Pa_{CO_2} using a mass spectrometer (Ohmeda MGM6000). Gas volumes were measured using a dry gas meter to enable $\dot{V}CO_2$ to be calculated. Simultaneously, a sample of radial arterial blood was taken for measurement of blood-gas tensions. From these values, fractional utilization (f) was calculated using the following formula [2]:

$$f = \frac{\dot{V}CO_2}{FGF \times Fa_{CO_2}}$$

The calculated values of f were plotted against $\dot{V}$E:FGF ratio (fig. 2).

The efficiency of the system improved with increasing $\dot{V}$E:FGF ratio, reaching a plateau of 0.7 at ratios greater than 1.5. The efficiency of the EAR is thus comparable to that of the T-piece [2].

ACKNOWLEDGEMENT

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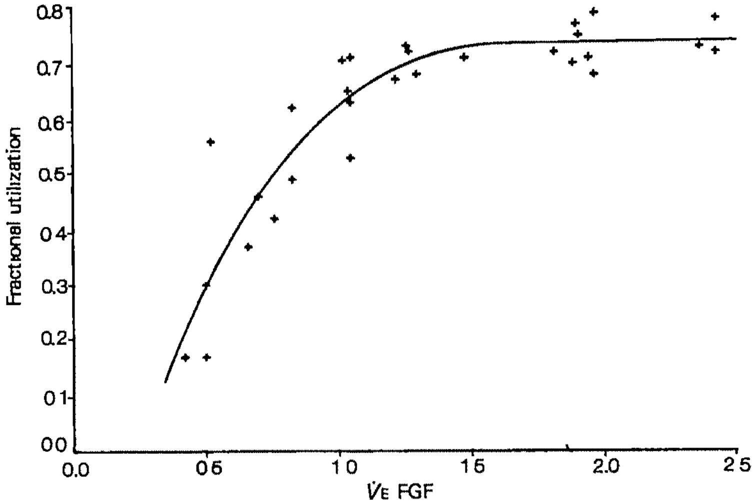

FIG. 2. Fractional utilization *vs* $\dot{V}$E:FGF ratio.

EFFECT OF SEDATION WITH ALFENTANIL, MIDAZOLAM OR PROPOFOL ON OXYGEN TRANSPORT VARIABLES IN THE CRITICALLY ILL

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One goal in the provision of oxygen to the respiring tissues is the independence of oxygen consumption (Vo_2) from the delivery (Do_2). If this is not the case, oxygen debt may ensue. The use of agents which adversely affect variables of oxygen transport, such as cardiac index (CI), arterial oxygen content (Ca_{O_2}) and mixed venous oxygen content ($C\bar{v}_{O_2}$), may tip the balance towards delivery-dependent oxygen consumption and hence multi-organ failure. We therefore tested alfentanil, midazolam or propofol (used for sedation in intensive care patients) for their effects on oxygen transport variables.

In a randomized study 30 patients requiring sedation during mechanical ventilation of the lungs in intensive care were allocated to three groups for sedation with alfentanil 2–5 mg h^{-1}, midazolam 1–3 mg h^{-1} or propofol 10–25 ml h^{-1}. All were receiving dobutamine i.v. by infusion CI, mean arterial pressure (MAP), total peripheral resistance (TPR), pulmonary vascular resistance (PVR), Do_2 and Vo_2 were measured and calculated immediately before and 1 h after infusion of drug (tables VI, VII). Pulmonary capillary wedge pressure was maintained at the pre-sedation value. There was no change in blood lactate concentration during the study period.

TABLE VI. *Effects of alfentanil, midazolam and propofol on cardiac index (CI), mean arterial pressure (MAP) and total peripheral resistance (TPR) (mean (SD)).* $*P < 0.05$; $**P < 0.01$

Group	CI (litre min^{-1} m^{-2})	MAP (mm Hg)	TPR (dyn cm s^{-5})
Alfentanil			
Before	4.8 (1.0)	92 (19)	1159 (483)
After	4.4 (0.9)**	85 (15)	1409 (477)**
Midazolam			
Before	3.9 (1.8)	86 (21)	1850 (1299)
After	3.8 (1.7)	88 (19)	1793 (1306)
Propofol			
Before	4.0 (1.7)	94 (22)	1900 (926)
After	3.7 (1.5)*	77 (18)**	1570 (770)*

TABLE VII. *Effects of alfentanil, midazolam and propofol on pulmonary vascular resistance (PVR), oxygen delivery (Do_2) and oxygen consumption (Vo_2) (mean (SD)).* $*P < 0.05$; $**P < 0.01$

	PVR (dyn cm s^{-5})	Do_2 (ml)	Vo_2 (ml)
Alfentanil			
Before	238 (96)	642 (144)	170 (27)
After	276 (95)**	569 (102)*	155 (32)*
Midazolam			
Before	302 (151)	511 (238)	152 (46)
After	325 (140)	522 (229)	151 (29)
Propofol			
Before	348 (167)	526 (239)	150 (36)
After	297 (146)**	455 (194)*	126 (34)**

PLASMA LEUCINE TURNOVER AND OXIDATION IN CRITICAL ILLNESS

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Information on the relationship between protein metabolism and the hormonal and metabolic state of severely ill patients is sparse. We have examined the kinetics of turnover of plasma leucine using tracer infusion, over 4 h, of L-(1-^{13}C)-leucine and mass spectrometric methods in six critically ill patients (1F:5M; ages 41–68 (median 53) yr; weights 63–118 (median 78.2) kg; APACHE II scores 11–31 (median 23); sepsis scores [1] 13–30 (median 18)) studied on nine occasions. Five patients were in renal failure. The results were compared with those obtained in four healthy volunteers (1F:3M; ages 43–57 (median 55) yr; weights 53.4–96.8 (median 73.7) kg).

Measurements of respiratory gas exchange were made and expired air collected for ^{13}C-carbon dioxide. Blood was taken every 1 h for enrichment of plasma α-keto-isocaproate and every 2 h for measurement of cortisol, growth hormone, glucagon and insulin.

Patients were studied 16 h after cessation of parenteral nutrition and 6 h after receiving 5% glucose if indicated clinically. Patients' lungs were ventilated mechanically and their cardiovascular systems were stable during the measurement.

Leucine flux (i.e. whole body protein breakdown) was increased in the patients compared with the healthy controls (leucine 90–213 (median 130) µmol kg^{-1} h^{-1} *vs* 30–95 (median 76) µmol kg^{-1} h^{-1}, respectively) ($P < 0.01$). Leucine oxidation also was increased compared with controls (11–34 (median 15) µmol kg^{-1} h^{-1} *vs* 5–18 (median 11) µmol kg^{-1} h^{-1}) ($P < 0.05$), as was synthesis of leucine (79–179 (median 111) µmol kg^{-1} h^{-1} *vs* 25–83 (median 63) µmol kg^{-1} h^{-1}) ($P < 0.02$). Both oxidation and synthesis of leucine, expressed as a proportion of flux, were similar in the two groups (oxidation: patients 13.6 (SD 2.7)%, controls 15.8 (2.1)%; synthesis: patients 86.4 (2.7)%, controls 84.2 (2.1)%).

There was a significant correlation between leucine flux and concentrations of both glucagon ($P < 0.01$) and cortisol ($P < 0.01$). There was no difference between the groups in concentrations of insulin or growth hormone. In three patients in whom flux was measured more than once, the two measurements differed by 5–38%.

There was no correlation between leucine flux and 24-h energy expenditure, percentage energy derived from protein oxidation, sepsis or APACHE II scores.

It is concluded that, in critical illness plasma cortisol and glucagon concentrations are directly related to leucine flux. We have not demonstrated a relationship between leucine flux and severity of illness, using existing techniques of assessing severity. Both protein breakdown and synthesis are increased, but protein is not increased in importance as a source of fuel relative to fat and carbohydrate.

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SPECTRAL HARMONIC CHANGES IN INTRACRANIAL PRESSURE WAVEFORM OCCURRING IN PATIENTS WITH INTRACRANIAL HAEMORRHAGE

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The intracranial pressure waveform (ICPWF) potentially provides more information than mean intracranial pressure (MICP). It is noted commonly to vary in morphology with differing intracranial conditions, although such changes are not necessarily reflected by MICP. Spectral analysis provides an objective method of quantifying changes in ICPWF morphology.

Animal studies suggest correlations between amplitude transfer functions and MICP [1], and a negative correlation between the centroid frequency of the ICPWF spectrum and the pressure–volume index [2]. These imply an increased frequency response of the intracranial cavity to arterial pulsations as intracranial compliance decreases.

This study derived some simple indices from ICPWF spectra measured in patients with intracranial haemorrhage, and compared them with clinical events and MICP.

Spectral analysis was applied to the ICPWF of 15 patients with head injury with presenting Glasgow Coma Scales (GCS) between 3 and 14. The patients were all admitted to the ICU after neurosurgery for insertion of an intraventricular catheter and removal of haematoma where appropriate. ICPWF and radial arterial pressure waveforms (APWF) were measured (Deseret 8060), the signals recorded (Hioki 8820 Hi Corder) and spectral analysis performed by Fast Fourier Transform.

ICPWF frequency spectra consisted of a series of harmonic components with a fundamental or first harmonic equal to that of the APWF. Neither centroid nor 90% spectral edge frequencies for the ICPWF correlated with MICP over a range of ICP from 6 to 87 mm Hg.

TABLE VIII *Comparison of harmonic counts for APWF (Na), ICPWF (Nc) and MICP for patients with differing Glasgow Coma Scale (GCS) on presentation*

	GCS on presentation		
	> 12	6–11	< 5
MICP (mm Hg)	19.8 (6.5)	20.9 (10.6)	54.5 (22.7)
Na	7.9 (1.5)	8.3 (2.7)	9.8 (1.8)
Nc	11.4 (2.6)	7.9 (1.9)	8.0 (2.5)
Na − Nc	$P < 0.05$	ns	$P < 0.05$

The mean spectral harmonic counts for the APWF (Na 8.5 (SD 2.3)) and for the ICPWF (Nc 8.5 (SD 2.7)) did not differ significantly for the total sample of patients, but when patients from the two extremes of severity of injury (GCS < 5 or GCS > 12 on presentation) were compared, it appeared that these may form two different subgroups: Na > Nc and Na < Nc (table VIII).

The APWF:ICPWF harmonic count ratio may provide a simple spectral index correlated with the severity of intracranial pathology. The harmonic count is related directly to ICPWF morphology as opposed to centroid or spectral edge frequencies, which are dependent on arterial pulse rate.

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EFFECT OF CARDIOPULMONARY BYPASS FLOW ON RENAL FUNCTION

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Cardiopulmonary bypass (CPB) may result in renal impairment. Some authors claim a high CPB flow is required to maintain renal function [1]; others have preserved renal function with low flow CPB [2].

We have studied prospectively 120 patients having coron-

TABLE IX. *Change in renal function (median (range)). Changes in creatinine concentration and clearance of creatinine calculated as (pre-CPB minus post-CPB)/pre-CPB (%)*

	Fixed-flow CPB	Variable-flow CPB
Change in creatinine concn (%)	+16 (−23 to +66)	+20 (−36 to +100)
Change in creatinine clearance (%)	+17 (−75 to +120)	0 (−76 to +82)
Peak post-op. concn of creatinine (mmol litre^{-1})	122 (+86 to +193)	125 (+94 to +200)

ary artery bypass surgery. A standardized anaesthetic technique was used, with non-pulsatile CPB using membrane oxygenators, moderate hypothermia, 20-μg arterial cannula filters, and infusions of mannitol and dopamine. Patients were allocated randomly to either a fixed CPB flow of 2.4 litre m^{-2} or a CPB flow varied to maintain a venous return oxygen saturation of 75–80 %, which has been reported previously to improve urine output during CPB [3]. Vasoactive drugs were given during CPB to maintain a mean arterial pressure of 50–80 mm Hg. Patients were assessed using creatinine clearances and by frequent measurement of blood-gas tensions and concentrations of lactate and electrolytes.

Whilst, overall, there was a postoperative decline in renal function, there was no significant difference between the two groups in this respect (table IX).

Multivariate analysis of variance was applied to help identify risk factors for renal impairment; these included patient age and mean perfusion pressure.

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MAY EXTRADURAL PRESSURE BE POSITIVE?

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The extradural space is a potential space where the dura is loosely applied to the spinal canal. Therefore, during entry into the extradural space, the dura must be pushed away from the vertebral canal with a force sufficient to overcome the outward pressure exerted by the cerebrospinal fluid (CSF).

Recently it was discovered that some of our Macintosh balloons were very soft. This may have resulted from prolonged storage or from autoclaving at a high temperature. During routine use, these balloons did not deflate when the needle entered the extradural space, and showed transmitted arterial pulsations. In order to monitor these phenomena on a video recorder, permission was obtained from five patients (aged 39–76 yr) receiving extradural analgesia for major gynaecological surgery. The patients were anaesthetized and were in the lateral position and receiving positive pressure ventilation of the lungs.

During entry into the extradural space, the balloon deflated rapidly in two patients. In one, deflation took a little more than 1 s and the balloon showed slight pulsations as it deflated. In two patients the balloons did not deflate, and transmitted arterial pulsations were seen in them; they were deflated forcibly by pinching. In all patients, 16-gauge Portex extradural catheters were inserted without any further advance of the extradural needle. The pressures in the five balloons ranged from 29 to 70 cm H_2O, the lowest being in the two that did not deflate.

Cardiogenic oscillations may originate from the proximity of a large artery. However, no such artery exists in the extradural space. The most likely origin of these pulsations is direct transmission from the dura. It is postulated that, when the extradural needle is in the extradural space, the pressure in the softer balloons is not sufficient to push the dura away from the spinal canal: the CSF pressure resists the inward movement of the dura. During laminectomy, the dura appears to be covered with a glistening liquid layer. It is likely that this layer produces a cohesive force between the dura and the vertebral canal, which may further resist the inward movement of the dura.

The video recording showed that a pressurized balloon may not deflate in the extradural space. After forcible deflation to overcome any cohesive/adhesive forces, the balloon may reinflate. From these observations one may infer that there is a positive pressure in the extradural space, created mainly by the outward pressure of CSF on the dura.

INCREMENTAL SPINAL ANAESTHESIA USING A 32-GAUGE CATHETER

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Continuous spinal anaesthesia has not been used widely because only relatively large-bore catheters have been available. A fine-bore 32-gauge catheter (TFX Medical) has been developed [1], and was used to investigate incremental spinal anaesthesia.

The project received Ethics Committee approval. Thirteen men, scheduled for transurethral resection of prostate or repair of inguinal hernias, gave informed consent. The 32-gauge catheter was placed through a 26-gauge Becton–Dickinson spinal needle, using an oblique paraspinous approach to L3–4 with the patient lying on his left side. Approximately 3 cm of catheter, which had a single hole at the end, was left in the subarachnoid space. The patient was then turned on to his back. Crystalloid 10 ml kg^{-1} was given i.v. before the first injection of 1–2 ml of 0.5 % plain bupivacaine. The response was assessed after 15 min by the segmental loss of sensation to cold. The block was re-assessed every 3 min, and increments of 0.5–1 ml were given if two successive assessments were at the same segment. Heart rate and arterial pressure were recorded at 3-min intervals.

There were technical problems with the catheter on three occasions as a result of failure to thread or to connect. In one patient, the onset of block was slow and block was not effective above L2. Regressing the height of the block against the logarithm of the dose [2] gave significant linear regres-

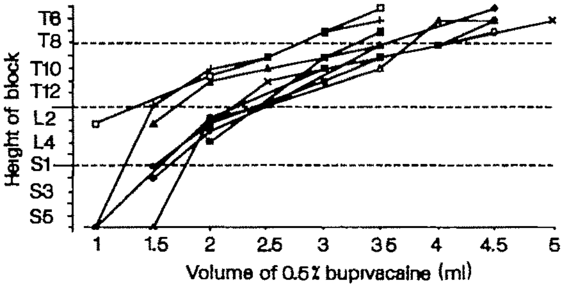

FIG. 3. Individual dose–response curves, segmental height of block *vs* volume of 0.5 % bupivacaine, for incremental spinal anaesthesia through a 32-gauge catheter.

sions for the remaining nine patients (fig. 3). The slope and intercept of each line did not correlate with the age, weight or height of the patient. The cardiovascular changes were small; the greatest observed decrease in systolic arterial pressure was from 200 mm Hg to 140 mm Hg.

On direct questioning the next day, no patient complained of headache.

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SEXUAL FANTASIES DURING MIDAZOLAM SEDATION

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Claims of sexual trespass while under benzodiazepine sedation have made headline news and have led to legal claims against dentists, four of whom have been deprived of the right to practice. A report of two personal experiences [1] led to a flow of similar reports, culminating in a second paper [2] which was reported widely in the media and, in turn, revealed further cases. Midazolam was used without opioids or other sedatives in 37 of 41 cases reported to this author.

There were 37 cases of possible fantasies or hallucinations, 29 in women. Of these, 23 occurred during sedation (14 dental; five endoscopy; four other) and six occurred during slow induction of anaesthesia. Twenty-five had some sexual element, 20 of which were unpleasant experiences.

In 16 of these the details of the events were verified by talking to the patient or their attendants or both; 13 were certainly fantasies. Although the events were very real to the patients and reported in a logical order, the presence of other persons or physical impossibility [2] confirmed that they could not have happened. If to these one adds the litigation cases, then 15 of 21 "incidents" were true fantasies. There was often difficulty in persuading patients that nothing improper had happened to them.

These unpleasant, distressing events "occurred" most frequently during dental sedation and oral endoscopy. Those during the slow induction of anaesthesia in young unpremedicated women were of a different nature. All appeared to be pleasurable and none complained of trespass.

In nine instances it was possible to see some connection between the complaint and an event occurring during sedation. The commonest was oral sex associated with dental work or oral endoscopy, while complaints of a "wandering hand" and fondling the breasts [2] could be associated with the attendant leaning over the patient while eliciting vital signs.

An earlier investigation has shown that all cases occurred with large doses of midazolam (more than 0.1 mg kg^{-1}) and a follow up revealed no incidents in more than 1000 patients given smaller doses [1].

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P6 ACUPUNCTURE ANTIEMESIS IN CANCER CHEMOTHERAPY: COMPARISON OF NEEDLING AND PERCUTANEOUS ELECTRICAL STIMULATION

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Under well controlled conditions in the perioperative period, a definite antiemetic action from direct stimulation of the P6 acupuncture (ACP) point has been demonstrated, with a less sustained effect from indirect stimulation [1]. The therapeutic value of P6 ACP as an adjuvant to standard antiemetics has also been shown in patients with sickness following cytotoxic drugs [2]. Since these latter patients would appreciate a non-invasive technique which, ideally, they could use themselves, transcutaneous electrical stimulation of P6 was studied as an alternative to P6 ACP.

All patients had experienced distressing sickness with a previous course of treatment despite the use of standard antiemetics, and some had previously been treated with ACP. Indirect stimulation of P6 was via a conducting stud using a battery operated d.c. stimulator, at a frequency of 10–20 Hz for 5 min. Current was increased until Chi (qi) was experienced. Treatment was given immediately before chemotherapy and standard antiemetics were continued. Patients evaluated the benefit on a four-point scale (A = complete relief to D = no benefit). A crossover study (direct and indirect stimulation) was possible only in 21 patients, other data being obtained from consecutive series.

TABLE X. *Frequency (%) of benefit from stimulation of P6 acupuncture point by needles (N) or transcutaneous electrical current (TC). n = number in group*

	Inpatients		Outpatients		Crossover	
	N	TC	N	TC	N	TC
n	89	113	43	89	27	27
Benefit						
A	75	50	74	40	85	40
B	24	29	12	39	15	27
C+D	1	21	14	21	0	33
P	< 0.0001		< 0.0008		< 0.0001	

In all series, invasive ACP had a better antiemetic effect than transdermal stimulation of P6 (table X). Although not as good as invasive ACP, transcutaneous electrical stimulation of P6 was of benefit to 77 % of patients when used as an adjuvant to standard antiemetics.

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PREOPERATIVE ST ABNORMALITIES DETECTED BY THE COMPAS AMBULATORY ECG MONITOR IN PATIENTS SCHEDULED TO UNDERGO PERIPHERAL ARTERIAL SURGERY

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Patients presenting for arterial surgery have a high incidence of ischaemic heart disease [1]. This study has investigated the incidence of ST abnormalities detected by the COMPAS (Cardiac Care Units Inc.) monitor in the preoperative period in this patient population.

We studied 29 patients presenting for various arterial surgical procedures. Ethics Committee approval and written patient consent were obtained. A full cardiac history and examination were carried out on the day before surgery. The preoperative ECG was analysed for ischaemic changes and chest x-ray evaluated for cardiomegaly and signs of heart failure. After the history and examination were obtained, the COMPAS monitor was applied; these are computerized ambulatory surveillance units programmed to detect and record ECG abnormalities [2]. The ECG algorithm depends on simultaneous recording of three standard leads (V2, V5 and AVF), with detection of any ST segment change lasting 30 s or more. A detailed account of ST events is downloaded onto a printer. Periods of ST depression or elevation of 2 mm or more were considered significant.

Mean (range) duration of monitoring was 21 h 31 min (8 h 17 min–46 h 27 min). No patient experienced chest pain during the preoperative period. In 20 of the 29 patients (69%) ST changes were detected by the COMPAS monitor. The incidence of ST changes in males ($n = 23$) was 70% and in females ($n = 6$) 67%. Mean (range) duration of ST segment abnormalities was 5 min per 1 h of monitoring (0 min–14 h). The association of preoperative factors with ST changes is shown in table XI.

Sixty-nine percent of the patients studied had ST changes in the preoperative period. It is likely that these ST changes represent silent myocardial ischaemia. These data suggest that the factors shown in the table may not be useful in prediction of preoperative ST changes.

TABLE XI. *Patients with ST changes (%). (No chest x-ray (CXR) available in five patients) MI = Myocardial infarction; CCF = congestive cardiac failure*

	Present		Absent	
Factor	%	*n*	%	*n*
Angina	71	7	68	22
Previous MI	57	7	73	22
Diabetes	60	5	71	24
Hypertension	70	10	68	19
Smoker	65	26	100	3
Signs of CCF	73	11	67	18
Preoperative ECG infarction	67	6	70	23
Preoperative ECG ischaemia	63	19	80	10
CXR cardiomegaly	83	6	61	18
CCF on CXR	100	3	62	21

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COMPARATIVE STUDY OF A STEPDOWN INFUSION OF PROPOFOL AND A LOW DOSE INFUSION SUPPLEMENTED BY BOLUSES

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Several schemes for infusion have been described for maintenance of anaesthesia with propofol [1, 2]. Newer infusion pumps allow rates of infusion capable of induction of anaesthesia and for bolus dosing. We have compared a three-stage manual stepdown regimen [1], with that of a steady low dose infusion supplemented by bolus doses for maintenance of anaesthesia.

TABLE XII. *Details of bolus dose requirement and cumulative dose in patients receiving propofol by steady rate or stepdown infusion for maintenance of anaesthesia.* * $P < 0.05$ *compared with steady rate at same time*

Time (min)	No. requiring bolus	Total no. of boluses	Cumulative dose (mg kg^{-1})
Steady rate			
0–10	8/23	11	3.10 (0.08)
10–20	17/23	9	4.47 (0.10)
20–30	3/21	5	5.63 (0.14)
30–40	7/20	11	6.91 (0.24)
Stepdown			
0–10	2/21	4	3.56 (0.09)*
10–20	6/21*	9	4.97 (0.10)*
20–30	4/20	10	6.08 (0.11)*
30–40	2/17	3	7.17 (0.23)

After Ethics Committee approval and informed consent were obtained, we studied 44 adult patients (mean (SD) age 44 (8) yr, ASA grade I–II). All patients were premedicated with temazepam 20 mg. Fentanyl 0.75 $\mu g\ kg^{-1}$ was given 5 min before induction of anaesthesia with propofol, which was infused using an Ohmeda 9000 pump at the rate of 600 ml h^{-1} until loss of verbal contact. Patients were allocated randomly to one of two groups: maintenance of anaesthesia in group 1 was with propofol 6 mg $kg^{-1}\ h^{-1}$; in group 2 it was with a step-down infusion of 10 mg $kg^{-1}\ h^{-1}$ for 10 min followed by 8 mg $kg^{-1}\ h^{-1}$ for 10 min and then maintained at 6 mg $kg^{-1}\ h^{-1}$. The propofol was infused with nitrous oxide and oxygen (2:1) in a Bain circuit. Bolus doses of propofol 20 mg were given to both groups as clinically indicated to maintain anaesthesia.

The dose requirements of propofol were recorded every 10 min and the heart rate and arterial pressures were recorded at baseline, 5 min after fentanyl and at 2, 5 and 10 min after induction of anaesthesia. Recovery times were recorded as time to opening the eyes and time to recalling the correct date of birth. The data were analysed for the dose required (Kruskal–Wallis), recovery times (Mann–Whitney *U* test) and for cardiovascular changes (repeated measures ANOVA).

There was no significant demographic difference between the groups. Eight patients experienced slight pain on injection of propofol. Apnoea occurred in 11 patients in the steady rate group, lasting 0.5–5 min (median 3.5 min), and in nine patients in the stepdown group, lasting 0.5–9.5 min (median 2.5 min) (ns). There were comparable decreases in systolic and diastolic arterial pressures and heart rate in both groups. There was no difference in recovery times between the groups and the total dose did not correlate with recovery. Significantly more bolus doses were required in the steady rate group, but a lower total dose was required in this group by 10, 20 and 30 min (table XII).

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OXYGEN SATURATION CHANGE DURING UPPER GASTROINTESTINAL ENDOSCOPY. USE OF SUPPLEMENTARY OXYGEN TO PREVENT DESATURATION

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Hypoxia occurs commonly during upper gastrointestinal (GI) endoscopy and predisposes patients to cardiac arrhythmias [1, 2]. The influence of i.v. sedation on oxygen saturation is uncertain; some studies suggest that desaturation occurs whether or not sedation is given [1]. We compared oxygen saturation and ECG changes during elective upper GI endoscopy following sedation, sedation with supplementary oxygen and no sedation.

Forty-five patients were allocated randomly to three groups: group 1 ($n = 11$) received neither sedation nor nasal oxygen before endoscopy; group 2 ($n = 16$) received midazolam 4.78 (SEM 0.28) mg before endoscopy; group 3 ($n = 18$) received midazolam 5.36 (0.25) mg and nasal oxygen 2 litre min^{-1} before endoscopy. Midazolam i.v. was administered to patients in groups 2 and 3 via a 21-gauge butterfly needle following topical anaesthesia of the oropharynx. Drug administration was discontinued when patients demonstrated objective signs of sedation. Monitoring included oxygen saturation and ECG. Data were recorded at baseline, insertion of mouth gag, insertion of endoscope, biopsy, removal of endoscope and 5 min after endoscopy. All endoscopies were carried out by the same endoscopist using an Olympus endoscope.

Statistical analysis included repeated analysis of variance (ANOVA). Data are expressed as mean (SEM).

The three patient groups were similar in weight and duration of procedure; there were significantly more females in each group. There was a significant difference in mean age between group 1 (40.3 (SD 5.0) yr) and group 2 (60.9 (4.0) yr), but not group 3 (51.7 (4.0) yr). Baseline oxygen saturation values did not differ between the three groups. Significant desaturation occurred at insertion of mouth gag, insertion of endoscope, biopsy and removal of endoscope in group 2 (midazolam alone) compared with groups 1 and 3 (fig. 4).

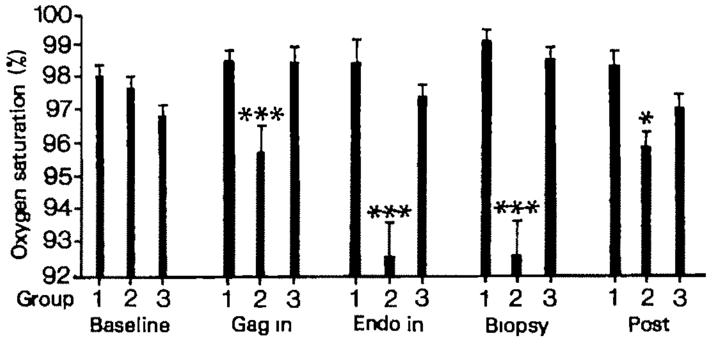

FIG. 4. Oxygen saturation in patients receiving neither sedation nor oxygen (group 1), midazolam sedation (group 2) or midazolam sedation plus supplementary oxygen (group 3): before endoscopy, at insertion of mouth gag, at insertion of the endoscope, at biopsy, at removal of endoscope and 5 min after endoscopy. $*P < 0.02$; $***P < 0.001$.

There was no significant difference in heart rate between the groups, and no arrhythmias were observed within the groups.

This study supports the hypothesis that arterial desaturation during upper GI endoscopy is linked directly to the use of i.v. sedation, and that supplementary oxygen is advisable when midazolam or similar drugs are used to facilitate endoscopy.

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CLINICAL EVALUATION OF FOAM-CUFFED TRACHEAL TUBES

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SURVEY OF DAY-CASE MORBIDITY BY DOMICILIARY ASSESSMENT

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Day-case anaesthesia is becoming used more frequently for "minor operations" on the grounds of economy and pressure of waiting lists. Most studies of day-case morbidity have relied on postal questionnaires for postoperative morbidity data [1–3].

We studied 28 dental patients (ASA grade I, aged 18–45 yr) on afternoon day-case lists admitted to a dedicated day-case ward. All gave signed, informed consent to participate in the study and were given a standard anaesthetic as part of another investigation. The normal day-case routine was otherwise left unchanged. All were anaesthetized using propofol, suxamethonium and spontaneous breathing of nitrous oxide in oxygen and isoflurane, supplemented by fentanyl 0.05 mg and droperidol 0.5 mg. Fourteen of the patients had also received i.v. dantrolene pretreatment.

Patients were visted at home by one of the investigators on both the first and second mornings after operation, between 10:00 and 12:00. At each visit, they were assessed and scored for a number of subjective indices of wellbeing. These included myalgia caused by suxamethonium (scored 0–5), pain from operation site (0–3) and daytime activity (0 = in bed to 3 = normal activity). They were also asked about any information which had been given to them concerning their admission. Four patients had been admitted to hospital overnight and one was still an inpatient at 48 h; these patients were assessed on the inpatient ward.

TABLE XIII. *Scores for subjective indices of wellbeing (range (median))*

	After operation	
	Day 1	Day 2
Total myalgia score (max 140)	30	37
Range	0–5 (0)	0–4 (0)
Pain at operation site (0–3)	1–3 (2)	0–3 (2)
Activity (0–3)	0–3 (1)	0–3 (2)

On the first day there was considerable morbidity (table XIII). Total myalgia score was 30 (maximum possible 140), but half the patients had received pretreatment with dantrolene. Jaw pain ranged from 1 to 3 (median 2). Only one patient was fit to return to work or resume normal daily activity.

By the second day there was some improvement. Total myalgia score was 37, but activity had improved considerably. Nevertheless, five patients were still in bed (one in hospital). However, only two further patients felt perhaps ready to resume work (but were still at home!).

We are concerned to have found that few patients knew the difference between analgesic and antibiotic tablets, fewer still could recall safety advice, and most patients seemed unable to return to work 48 h after "minor surgery".

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BETA-ADRENOCEPTOR BLOCK AFFECTS ONLY HEART RATE RESPONSE TO LARYNGOSCOPY AND INTUBATION IN HYPERTENSIVE PATIENTS

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Haemodynamic responses to laryngoscopy and intubation may be exaggerated in hypertensive patients, in whom significant increases in heart rate (HR) and systolic arterial pressure (SAP) may result in myocardial ischaemia. Both chronic and acute beta-adrenoceptor block may be useful adjuncts in preventing these changes [1, 2].

In the present study, we compared the responses in 31 normotensive patients (group N), 20 treated hypertensive patients receiving beta-blocking therapy (group B), and 19 untreated or diuretic-treated mildly hypertensive patients (group UT) (three arterial pressures recorded on the ward before operation as between 160/90 and 200/100 mm Hg). Patients were aged 31–74 yr.

After premedication with either an oral benzodiazepine or i.m. opioid and vagolytic drug, baseline readings were taken. Fentanyl 100–200 μg was administered and anaesthesia induced with thiopentone 4–5 mg kg^{-1}. Vecuronium 0.1 mg kg^{-1} was given 3 min after induction and the trachea intubated at 5 min, patients breathed 67 % nitrous oxide in oxygen supplemented by enflurane ($\leqslant$ 1 %). HR and arterial pressure were recorded non-invasively (DINAMAP 845XT) at 1-min inter-

TABLE XIV. *Mean (SD) baseline haemodynamic data and absolute changes during laryngoscopy and intubation (L + I) in normotensive patients (group N), untreated, mildly hypertensive patients (group UT) and hypertensive patients receiving beta-blocking therapy (group B)*

	Baseline	Response to L+I	P
Group N			
SAP (mm Hg)	131 (14)	+21 (9)	< 0.001
HR (beat min^{-1})	81 (15)	+19 (12)	< 0.001
SV (ml)	73 (18)	−16 (16)	< 0.02
SVR (mm Hg litre min^{-1})	18.1 (5.4)	+5.5 (4.0)	< 0.001
Group UT			
SAP (mm Hg)	166 (18)	+31 (31)	< 0.002
HR (beat min^{-1})	86 (15)	+18 (16)	< 0.002
SV (ml)	68 (16)	−13 (13)	< 0.004
SVR (mm Hg litre min^{-1})	22.0 (7.6)	+7.2 (4.5)	< 0.001
Group B			
SAP (mm Hg)	160 (20)	+29 (17)	< 0.002
HR (beat min^{-1})	66 (10)	+9 (8)	< 0.002
SV (ml)	79 (19)	−8 (8)	< 0.004
SVR (mm Hg litre min^{-1})	23.7 (8.4)	+6.9 (4.3)	< 0.002

vals; stroke volume (SV) and cardiac output (Q) were obtained by thoracic bioimpedance. Comparison of haemodynamic data obtained during laryngoscopy and intubation with baseline values was made using ANOVA and Mann–Whitney U test.

Induction of anaesthesia decreased SAP and Q in all groups ($P < 0.01$); SV decreased in groups N and UT ($P < 0.01$); SVR decreased in group B ($P = 0.01$). Decreases in SAP were greater in groups B and UT ($P < 0.01$); the decreases in Q were similar in all groups. The decrease in SVR in group B was greater than in groups N and UT ($P < 0.02$).

Laryngoscopy and intubation increased SAP, HR and SVR and decreased SV. The increase in HR was greater in groups N and UT ($P < 0.04$), while the decrease in SV was greater in group N compared with group B ($P < 0.01$) (table XIV).

Patients in group B exhibited substantially slower resting HR and a smaller increase to laryngoscopy and intubation than those in group UT. In all groups, the main pressor response to intubation appears to be an alpha-receptor mediated increase in SVR, and an accompanying decrease in SV.

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CARDIOVASCULAR EFFECTS OF ETOMIDATE, THIOPENTONE OR AN ETOMIDATE–MIDAZOLAM MIXTURE

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Etomidate causes minimal cardiovascular depression, but is associated with a high incidence of excitatory phenomena [1]. Midazolam effectively reduced side effects while maintaining

TABLE XV. *Changes in cardiac index (CI), mean arterial pressure (MAP) and heart rate (HR) (mean (SD)). Changes from baseline compared with etomidate:* *$P < 0.05$; **$P < 0.01$

		Time after induction (min)			
	Baseline	1	3	5	7
HR (beat min^{-1})					
Group 1	73 (13)	80 (11)**	84 (12)*	80 (13)	78 (15)
Group 2	78 (17)	78 (17)	78 (16)	76 (16)	78 (14)
Group 3	69 (15)	74 (15)	79 (17)	77 (15)	72 (17)
MAP (mm Hg)					
Group 1	110 (17)	110 (20)	103 (24)	106 (25)	100 (21)
Group 2	114 (16)	122 (22)	124 (23)	119 (27)	116 (30)
Group 3	113 (17)	119 (24)	114 (24)	109 (18)	105 (17)
CI (litre min^{-1} m^{-2})					
Group 1	2.9 (0.8)	2.7 (0.7)	2.3 (0.5)**	2.5 (0.8)	2.7 (0.9)
Group 2	2.8 (1.2)	2.8 (0.9)	3.0 (1.2)	2.9 (1.5)	2.9 (1.2)
Group 3	3.1 (1.0)	3.3 (1.1)	2.6 (0.9)*	2.7 (1.0)	2.3 (0.8)*

cardiovascular stability when used with ketamine (ratio 1:20) at induction of anaesthesia [2]. We have examined the effects of an etomidate–midazolam mixture in a similar ratio.

Following Ethics Committee approval, informed consent was obtained from 60 unpremedicated surgical patients. Cardiac output (CO) was measured continuously using a non-invasive monitor, NNCOM3, based on thoracic impedance. Mean arterial pressure (MAP) and heart rate (HR) were measured using a Dinamap. After baseline readings were obtained, patients were allocated randomly to three groups: group 1 = thiopentone; group 2 = etomidate; group 3 = etomidate 20 mg + midazolam 4 mg mixture. The agents were injected until loss of the eyelash reflex and anaesthesia maintained using further increments as necessary. Cardiac variables, ventilatory frequency, end-tidal carbon dioxide concentration and oxygen saturation were recorded at 1-min intervals.

The mean (SD) induction doses were 5.2 (1.0) mg kg^{-1} in group 1, 0.27 (0.04) mg kg^{-1} in group 2 and etomidate 0.29 (0.10) mg kg^{-1} + midazolam 0.048 (0.017) mg kg^{-1} in group 3. The changes in cardiac index (CI), MAP and HR are shown in table XV. Thiopentone caused a significant increase in HR and decrease in MAP compared with etomidate. Etomidate and etomidate–midazolam caused little change in HR and MAP. Thiopentone and etomidate–midazolam caused a significant decrease in CI compared with etomidate. Thiopentone values recovered towards baseline, but further increments of etomidate–midazolam were associated with a significant decrease in CI compared with etomidate alone.

The addition of low dose midazolam only minimally affects the cardiovascular stability of etomidate, while significantly reducing the number of unsatisfactory side effects.

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ENHANCEMENT OF BUPIVACAINE TOXICITY BY THERAPEUTIC PLASMA CONCENTRATIONS OF DILTIAZEM IN THE ANAESTHETIZED DOG

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Bupivacaine elicits negative inotropic and dromotropic effects in heart [1] and cardiovascular complications have been associated with inadvertent i.v. administration of this local anaesthetic. Verapamil, a calcium entry blocker (CEB) with pronounced cardiac depressant and local anaesthetic activity, potentiates the cardiovascular toxicity of bupivacaine in conscious dogs [2]. We investigated if an increased risk of cardiovascular depression occurs in the presence of clinical concentrations of diltiazem, a CEB that possesses minimal local anaesthetic activity and has a haemodynamic profile different from that of verapamil.

Studies were performed in open-chest, anaesthetized dogs. Anaesthesia was maintained with pentobarbitone, fentanyl and pancuronium. The study was conducted in compliance with local animal experimentation legislation. Following instrumentation and a period for stabilization (30 min), haemodynamic parameters and A–V nodal conduction times were measured before (baseline values) and at 10, 20 and 30 min after the sequential administration of three doses of bupivacaine as a loading dose (200, 400 and 600 μg kg^{-1}) followed by an i.v. infusion (25, 100, 200 μg kg^{-1} min^{-1}, respectively) for 30 min. Thereafter, bupivacaine was infused at 400 μg kg^{-1} min^{-1} and plasma concentrations of bupivacaine and haemodynamic parameters were measured every 10 min until each animal died. A control group of animals ($n = 6$) received only bupivacaine. A second group ($n = 7$) received diltiazem 400 μg kg^{-1} followed by an infusion of 12 μg kg^{-1} min^{-1} throughout the experiment. When stable plasma concentrations of diltiazem were achieved (250 (SEM) 20 μg $litre^{-1}$), bupivacaine was administered as in control animals.

Toxicity of bupivacaine was enhanced in the presence of diltiazem; lethal plasma concentrations of bupivacaine were significantly ($P < 0.01$) greater in control animals (13.4 (4.2) *vs* 7.1 (1.8) mg $litre^{-1}$). Plasma concentrations of bupivacaine following 30-min infusions at the three doses were similar in control (1.3 (0.1), 3.3 (0.2) and 5.8 (0.9) mg $litre^{-1}$) and diltiazem-treated groups (1.0 (0.1), 2.8 (0.2) and 7.5 (0.2) mg $litre^{-1}$). In both groups, these three doses of bupivacaine produced similar depressions of cardiac index (CI), left ventricular (LV) segmental work and $LVdP/dt$; concentrations causing a 50% reduction from baseline (ED_{50}) were in the range 4–7 mg $litre^{-1}$ and were not different between groups. In control animals, systemic vascular resistance index (SVRI) was significantly increased by these concentrations of bupivacaine, so that mean arterial pressure (MAP) remained unchanged. In diltiazem-treated animals, SVRI that was reduced (to 80% of baseline) by diltiazem *per se*, was increased less and MAP was not maintained. The lower SVRI (afterload) in the diltiazem-treated group at each plasma concentration of bupivacaine concealed a significantly greater cardiac depression that was not detectable by the measured (afterload-dependent) indices of cardiac function. In addition, greater depression of A–V nodal conduction was demonstrable in animals treated with a combination of diltiazem and bupivacaine.

In control animals, at near fatal concentrations of bupivacaine (10–14 mg $litre^{-1}$), progressive increases in SVRI were accompanied by further decreases in CI, hypotension and death as a result of ventricular arrhythmias. In diltiazem-treated animals, death, which occurred at smaller concentrations of bupivacaine (4–8 mg $litre^{-1}$), was caused by marked hypotension, cardiac failure and asystole.

Thus, in the anaesthetized dog, bupivacaine-induced depression of cardiac contractility and impulse conduction was enhanced in the presence of therapeutic concentrations of diltiazem. The margin of safety for bupivacaine was reduced approximately two-fold. Although additional investigation is warranted, we suggest that bupivacaine toxicity may be enhanced in patients receiving diltiazem.

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EFFECT OF SPEED OF INJECTION ON THE DOSE REQUIRED TO INDUCE ANAESTHESIA WITH PROPOFOL

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The manufacturer's recommended induction dose of propofol is 2.5 mg kg^{-1} injected at 40 mg/10 s. It has been our impression that the dose required is smaller, with a slower rate of injection, as suggested also by the results of a paper studying three different rates of injection [1]. However, in that study, a dose of 2.5 mg kg^{-1} was administered, even when induction was achieved before all the dose was injected. This study was undertaken to establish the rate of injection which combines the "sleep dose" of propofol (the dose required to obtund the eyelash reflex) with a satisfactory induction of anaesthesia.

We studied 90 ASA group I patients aged 16–55 yr undergoing minor elective surgery. They were allocated randomly to one of three groups to receive propofol at: 20 mg every 5 s (group A), 10 mg every 5 s (group B), or 5 mg every 5 s (group C), until a sleep dose had been administered. All patients received temazepam 20 mg orally approximately 1 h before induction of anaesthesia.

Arterial pressure and arterial oxygen saturation were recorded throughout the period of induction with a Dinamap automatic arterial pressure recorder and a pulse oximeter (Datex Satlite). Propofol was injected at the specified rate until anaesthesia was induced. Spontaneous complaints of pain on injection were recorded. Induction of anaesthesia was determined at the point at which the patient could no longer hold in the air a 20-ml syringe filled with saline [2].

The patients breathed spontaneously 70 % nitrous oxide in oxygen supplemented with 3 % enflurane. Periods of apnoea of longer than 60 s were terminated by manual ventilation with the face-mask until the return of spontaneous breathing. Induction of anaesthesia was graded overall as good (totally smooth), satisfactory (spontaneous movement, easily controlled) or poor (any incidence of cough or problem with the airway).

Statistical analysis was by analysis of variance and Student's *t* test for comparison of doses and duration of apnoea and chi-square for comparison of pain and quality of induction. $P < 0.05$ was regarded as significant.

There was no statistical difference between the age or physical characteristics of the patients. There were significant differences between all three doses of propofol required to induce anaesthesia (table XVI). There was no statistical difference between the groups with respect to the incidence of pain experienced on injection, nor the duration of apnoea. The quality of induction was good or satisfactory in 96.7 % of patients in group A, 93.3 % of patients in group B and 88 % of patients in group C (ns).

TABLE XVI. *Details of patients studied, dose of propofol required to obtund the eyelash reflex (sleep dose), incidence of pain on injection and duration of apnoea (mean (SD)). ns = Not significant; **P < 0.01*

	Group A Propofol 20 mg/5 s		Group B Propofol 10 mg/5 s		Group C Propofol 5 mg/5 s
Age (yr)	34.6 (14.2)		32.5 (10.6)		30.1 (12.2)
Weight (kg)	69 (12)		75 (16)		70 (13)
Height (cm)	169 (9)		172 (9)		172 (9)
Sex (M/F)	13/17		17/13		16/14
Sleepdose (mg kg^{-1})	2.64 (0.37)	**	1.97 (0.37)	**	1.61 (0.34)
Pain (%)	29	(ns)	36	(ns)	23.3
Apnoea (s)	34 (46)	(ns)	28 (39)	(ns)	12 (16)

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RECOVERY FROM OUTPATIENT ANAESTHESIA: COMPARISON OF TOTAL I.V. ANAESTHESIA WITH AN INHALATION TECHNIQUE

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Incremental doses of propofol in combination with nitrous oxide is a suitable anaesthetic for day surgery and is associated with rapid psychomotor recovery [1]. We have compared recovery from a total i.v. anaesthetic (TIVA) technique using propofol and alfentanil with an inhalation technique.

Following Ethics Committee approval and informed consent, 50 patients undergoing dilatation and curettage as outpatients were assigned randomly to one of two equal groups. All were aged between 16 and 60 yr, ASA I or II, and none was taking psychoactive drugs. No premedication was given.

Anaesthesia was induced in the TIVA group with alfentanil 0.5 mg and propofol 2 mg kg^{-1}, and maintained with 10-mg increments of propofol. Oxygen 100 % was administered. Induction was the same in the inhalation anaesthesia group, but maintenance was with 67 % nitrous oxide in oxygen and 1–3 % isoflurane. Critical Flicker Fusion Threshold (CFFT) and six-Choice Reaction Time (CRT) were measured before operation and at 1 and 2 h after operation. Data were analysed using the Wilcoxon signed rank test.

Demographic data for the two groups were similar. Mean duration of anaesthesia was 8.1 min for the TIVA group and 10.1 min for the isoflurane group. The mean rate of administration of propofol in the TIVA group was 194 µg kg^{-1} min^{-1}.

CFFT was significantly ($P = 0.0001$) decreased 1 h after operation in both groups (table XVII). After 2 h there was no significant change in CFFT in the TIVA group, but a signi-

TABLE XVII. *CFFT and CRT (mean (SD)).* **Significant change from baseline* ($P < 0.05$)

	TIVA group	Isoflurane group
CFFT (Hz)		
Preop.	30.3 (2.5)	28.9 (2.4)
1 h postop.	27.9 (2.0)*	26.5 (2.7)*
2 h postop.	29.2 (2.1)	27.2 (2.8)*
CRT, total (ms)		
Preop.	622 (95.7)	690 (173)
1 h postop.	665 (85)*	833 (302)*
2 h postop.	608 (77)	717 (173)*

ficant ($P < 0.05$) decrement in the isoflurane group. CRT increased significantly ($P < 0.02$) 1 h after operation in the TIVA group, but had returned to baseline at 2 h. In the isoflurane group, CRT was still significantly ($P < 0.05$) prolonged at 2 h.

This study shows that the time scale of psychomotor recovery from a total i.v. anaesthetic technique using propofol and alfentanil is shorter than that from inhalation anaesthesia using nitrous oxide in oxygen and isoflurane.

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POSTER PRESENTATIONS

EFFECT OF THE TRENDELENBURG POSITION ON LOWER OESOPHAGEAL SPHINCTER PRESSURE

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Alteration of position from supine to lithotomy reduces lower oesophageal sphincter pressure (LOSP) significantly without changing intragastric pressure [1]. Increasing intra-abdominal pressure during peritoneal insufflation in the lithotomy position increases intragastric pressure and LOSP [2], but the effect of the Trendelenburg position alone has not been assessed.

With approval from the Ethics Committee and informed consent, we studied 10 healthy patients undergoing gynaecological surgery. Anaesthesia was standardized: premedication comprised diazepam 10 mg orally 2 h before operation, induction with thiopentone 4 mg kg^{-1} followed by atracurium 0.4 mg kg^{-1} and fentanyl 1.5 µg kg^{-1} and maintenance with 70 % nitrous oxide and 0–1 % enflurane in oxygen with ventilation to normocapnia.

When stable anaesthesia had been achieved, the previously calibrated oesophageal manometry tube, connected via a preamplifier to a multi-channel chart recorder, was passed into the stomach. Recordings were made of intragastric (GP), LOSP and oesophageal pressures at the end of expiration by the pull-through technique [3]. Barrier pressure (BrP) was calculated as LOSP − GP.

Control measurements were taken in the supine position. Measurements were repeated in the 15° and 30° head-down positions for 3 min at 1-min intervals. The apparatus was checked for zero and calibration drift at the end of each study.

TABLE XVIII. *Mean (SEM) changes in gastrointestinal pressures (cm H_2O) associated with 15° and 30° head-down Trendelenburg positions.* *$P < 0.05$

Pressure	Head-down tilt 15°	Head-down tilt 30°
Gastric	0.80 (0.36)	1.20 (0.35)*
LOSP	−2.10 (2.10)	−2.8 (1.30)
BrP	−2.86 (2.25)	−0.67 (1.34)

Results were analysed using Student's *t* test for paired data comparing the Trendelenburg position with supine measurements.

Although GP was increased statistically in the steep Trendelenburg position, the magnitude was not clinically significant. However, LOSP and BrP were unchanged in the head-down position (table XVIII), and therefore this position should not predispose to regurgitation in normal patients.

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EFFECT OF I.V. LIGNOCAINE ON THE CARDIOVASCULAR AND CATECHOLAMINE RESPONSES TO LARYNGOSCOPY AND INTUBATION

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The effect of varying the time of prior administration of i.v. lignocaine on the cardiovascular responses to laryngoscopy and intubation has been studied previously, with conflicting results [1, 2]. We have re-examined this question by measuring cardiovascular and catecholamine responses to tracheal intubation in a group of ASA I patients.

After Ethics Committee approval, consent was obtained from 40 healthy patients undergoing gynaecological procedures requiring tracheal intubation. Premedication comprised morphine 0.1 mg kg^{-1} and prochlorperazine 0.2 mg kg^{-1}. Patients were allocated randomly to four groups: a control group (group 1), and three groups receiving i.v. lignocaine 1.5 mg kg^{-1} 2 min (group 2), 3 min (group 3) and 4 min (group 4) before laryngoscopy. Anaesthesia was induced with thiopentone 4–5 mg kg^{-1} and vecuronium 0.1 mg kg^{-1} and maintained with 66 % nitrous oxide and 1 % enflurane in oxygen. Laryngoscopy was performed 4 min after induction.

Monitoring consisted of non-invasive arterial pressure, ECG, capnometry and pulse oximetry. Measurements of heart rate and arterial pressure, and blood samples for plasma concentrations of catecholamines were taken before induction and at 1, 3 and 5 min after intubation.

TABLE XIX. *Mean* (SEM) *percentage change from pre-induction to 1 min after laryngoscopy for heart rate (HR) and mean arterial pressure (MAP)*

	Group 1	Group 2	Group 3	Group 4
HR (% change)	+21.7 (6.5)	+21.7 (8.7)	+21.7 (9.6)	+25.7 (7.3)
MAP (% change)	+19.1 (4.8)	+7.7 (4.6)	+3.1 (8.9)	−0.05 (5.7)

Heart rate increased significantly 1 min after intubation in all groups by 21–26% compared with pre-induction values; analysis of variance failed to show significant differences between groups. Mean arterial pressure increased from before induction to 1 min after laryngoscopy in groups 2 and 3, but was unchanged in group 4. In group 1 there was a significant increase of 19.1% which was significantly different from the change in the other three groups (table XIX). All haemodynamic parameters decreased from 1 min after laryngoscopy and did not differ between groups at 3 and 5 min after induction. The changes in catecholamine concentrations did not differ significantly between groups.

We conclude that i.v. lignocaine 1.5 mg kg^{-1} given at least 4 min before laryngoscopy may attenuate completely the pressor, but not the chronotropic, response to laryngoscopy and intubation. This suggests that lignocaine may not be the agent of choice for attenuating the sympathoadrenal responses to laryngoscopy and intubation in patients with myocardial ischaemia.

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METABOLIC EFFECTS OF DOBUTAMINE

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Dobutamine is used in critically ill patients for cardiovascular support. Catecholamines have significant metabolic effects, stimulating glycogenolysis, lipolysis and whole body oxygen consumption, but there are no data on the metabolic effects of dobutamine in normal man.

After an overnight fast, eight male volunteers (median age 32 yr, range 22–42 yr) were allocated randomly to receive, i.v., dobutamine in 5% glucose at 2, 5 and 10 µg kg^{-1} min^{-1} for three consecutive periods of 45 min each or the corresponding volume of glucose solution alone. Blood was taken before infusion, 30 and 45 min from the start of each infusion period, and 15 and 30 min after cessation of the infusion for adrenaline, noradrenaline, dopamine, glucose, glycerol, free fatty acids (FFA) and insulin. Oxygen consumption was measured using a ventilated canopy. Arterial pressure was measured every 5 min; ECG was monitored. Glycerol and FFA increased significantly in step with the dobutamine infusion ($P < 0.001$): at 10 µg kg^{-1} min^{-1}, glycerol increased by 250%, and FFA by 350%. Insulin increased significantly at the 5- and 10-µg kg^{-1} min^{-1} infusion rates ($P < 0.01$). Blood concentration of glucose decreased significantly ($P < 0.05$). Adrenaline and noradrenaline concentrations both decreased significantly ($P < 0.05$) and returned to pre-infusion values when the infusion stopped. Dopamine concentration remained less than 0.1 nmol litre^{-1}. Oxygen consumption (Vo_2) also increased in step with the rate of infusion of dobutamine; at the 10 µg kg^{-1} min^{-1} infusion rate Vo_2 was increased by 33.9% ($P < 0.0005$). Respiratory quotient decreased in a stepwise manner, from 0.85 to 0.77 ($P < 0.0001$). Systolic arterial pressures increased significantly ($P < 0.01$), even at the 2-µg kg^{-1} min^{-1} rate ($P < 0.05$).

It is concluded that dobutamine has significant metabolic effects. It increases Vo_2 to a greater extent than dopamine [1] and is a potent lipolytic agent, but the effects observed on glucose and catecholamine metabolism are the opposite of those seen with dopamine.

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EFFECT OF MOTION ARTEFACT ON THE FUNCTION OF FOUR PULSE OXIMETERS

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Pulse oximetry is emerging as a standard in clinical monitoring. However, the present generation of pulse oximeters suffer from a number of limitations [1]. The response of the Ohmeda 3700, Nellcor 200, Datex Satlite Plus and the Simed S100 pulse oximeters to induced hypoxaemia in the presence of motion artefact was assessed, using an industrial vibration facility.

Following Ethics Committee approval and informed consent, we studied five healthy male volunteers (mean age 35 yr). The subject rested comfortably, seated in a chair, with the left arm placed across the top of the vibration platform. The arm was loosely held in a preformed support and the oximeter probes were applied to the fingers of the left hand. The thumb was not used and ECG electrodes were applied and connected to the two oximeters with ECG linkage.

A control/safety probe was attached to the index finger of the right hand. The outputs from the oximeters were recorded on a chart recorder, the platform was vibrated at 4 Hz sine wave and 8 Hz bursts using a vertically mounted, hydraulically driven actuator of 10 t static capability and a maximum stroke of + and −75 mm working at a pressure of 14.7 bar. The frequency and amplitude of vibration were monitored using a LVDT displacement transducer.

TABLE XX. *Occurrence of* $>5\%$ *reduction in* Sa_{O_2} *on starting vibration. McNemar's test:* $^{*}P < 0.01$

Instrument	Non-vibrated	4 Hz	8 Hz
Ohmeda 3700	0/20	13/20*	12/20*
Nellcor N200	0/20	1/20	1/20
Satlite	0/20	3/20	4/20
Simed	0/20	7/20*	10/20*

The motion artefact produced delays in the detection of hypoxaemia, heart rate abnormalities and spurious decreases in Sa_{O_2} reading. The instruments under test behaved differently and there were clearly finger-dependent effects.

All instruments produced a prolonged detection time during the vibration sequences; this reached significance at 4 Hz using the Ohmeda 3700 oximeter on the 1st, 3rd and 4th fingers and using the Simed oximeter on the 1st and 2nd fingers. At 8 Hz vibration, significant delays in detection time were found using the Ohmeda 3700 on the 1st, 3rd and 4th fingers, using the Simed oximeter on the 1st, 2nd and 4th fingers and with the Satlite Plus oximeter on the 1st and 4th fingers.

The 4-Hz sine wave vibration produced heart rate discrepancies in the Ohmeda 3700 and Simed S100 oximeters. The Nellcor 200 and the Satlite Plus oximeters did not display any significant increases in heart rate discrepancies during the 4-Hz sine wave vibration.

A significant, $>5\%$, reduction in Sa_{O_2} output from the Ohmeda 3700 oximeter occurred at the start of the 4-Hz and the 8-Hz vibration sequences (table XX). This was sustained until the vibration ceased, at which point it gradually recovered. The Simed oximeter also produced significant reductions in the indicated Sa_{O_2} at the 4-Hz and 8-Hz vibration.

Motion artefact produced significant increases in the detection time for hypoxaemia in some of the oximeters tested, and also produced heart rate discrepancies, especially in oximeters without ECG linkage, and spurious decreases in the Sa_{O_2} output which were sustained until the vibration stopped.

There was a marked difference in susceptibility to motion artefact between the fingers, the smaller fingers being most susceptible.

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CENTRAL ENHANCEMENT OF EVOKED ELECTROMYOGRAPHY

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Evoked electromyographic (EEMG) monitoring of neuromuscular block is unreliable because the first response of the train-of-four often fails to return to the control value during recovery. One explanation is the modification during anaesthesia of a central mechanism responsible for "muscle reactivity" [1]. This hypothesis has not been substantiated, although it has been quoted to explain the failure of EEMG monitoring [2, 3].

EEMG monitoring was performed using two Datex NMT100 Relaxographs and foam-based electrodes (Nikomed 4570). Calibration of the Relaxographs was performed with the subject awake.

Volunteer study. EEMG monitoring was performed on both arms of four healthy adult males: ulnar nerve stimulation at the wrist produced a response recorded over the first dorsal interosseous muscle. To reduce movement artefact, each hand was held in a fist, thumb on the outside, by a piece of 10-cm elastoplast. The Relaxographs were calibrated and recordings of the EEMG were made from both arms for 10 min. An ulnar nerve block was then performed at one elbow using 2% lignocaine with adrenaline 1:200000 6 ml. Recordings of EEMG from both arms were continued for 30 min after the nerve block.

Patient study. Fifteen patients scheduled to undergo transurethral resection of the prostate under subarachnoid block were studied 90–120 min after premedication with temazepam 10–20 mg. EEMG monitoring was performed on the left leg: posterior tibial nerve stimulation at the medial malleolus produced a response recorded over the flexor hallucis brevis. The Relaxograph was calibrated and a 5-min control recording was made. The patient was turned to the left lateral position for induction of subarachnoid anaesthesia with 0.5% bupivacaine in 8% glucose 3.5 ml injected at the L2–3 or L3–4 interspace. Patients were immediately returned to the supine position and the recording was continued for a further 30 min.

Clinically complete motor and sensory paralysis of the ulnar nerve was obtained in all volunteers, and a bilateral motor and sensory block was produced to at least T10 in every patient. There was no significant change in the EEMG response during subarachnoid block or ulnar nerve block, nor in the unblocked arms of the volunteers.

This study has not demonstrated a central enhancement effect; the lack of agreement with the observations of Paloheimo and Rantala [3] requires further explanation. A central neural mechanism is unlikely to modify the endplate response to supramaximal stimulation of the lower motor neurone, as this neurone is the final common neural pathway to the motor endplate.

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DYNAMIC–KINETIC RELATIONSHIPS FOR SUFENTANIL DURING NITROUS OXIDE–OXYGEN ANAESTHESIA

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We have reported previously the haemodynamic effects and disposition of sufentanil administered in doses of 0.4–2.5 $\mu g\ kg^{-1}$ to supplement nitrous oxide [1, 2]. We have re-analysed some of these data to determine the concentration of sufentanil in combination with nitrous oxide that suppresses noxious stimuli during surgery in 50% of patients ($SFC_{P,50}$:S), and $SFC_{P,50}$ for adequate spontaneous ventilation and extubation.

We studied 33 patients (ASA I, II; aged 26–66 yr) undergoing abdominal or major body surface surgery after premedication with diazepam. Anaesthesia was induced with thiopentone 3–4 mg kg^{-1} and, following intubation facilitated by vecuronium 0.1 mg kg^{-1}, was maintained with 67% nitrous oxide. Patients received sufentanil 0.4, 1.0 or 2.5 μg kg^{-1} after induction of anaesthesia. Further supplementation was given only if there were signs of inadequate anaesthesia: systolic arterial pressure $>20\%$ greater than pre-induction value, heart rate >90 beat min^{-1}, sweating, lachrymation or somatic movement. Venous blood for measurement of plasma concentrations of sufentanil (by radioimmunoassay) was sampled at incision, at extubation, and at times of inadequate anaesthesia, maximal surgical stimulation, or both. $SFC_{P,50}$ was determined by logistic regression using a model of the form:

$$\text{probability} = SFC_P{}^{\gamma}/(SFC_{P,50}{}^{\gamma}+SFC_P{}^{\gamma})$$

Twenty-eight patients showed no response to the initial incision (sufentanil concentration range 0.07–2.81 ng ml^{-1}). Plasma concentration of sufentanil in responders was 0.07–0.54 ng ml^{-1}.

Inadequate anaesthesia occurred during surgery in 23 patients at plasma concentrations of sufentanil between 0.04 and 0.54 ng ml^{-1}. $SFC_{P,50}$:S was 0.29 ng ml^{-1} (95% CI 0.19–0.40); the slope of the concentration–response curve (γ) was 1.91 (SEM 0.57). In 29 patients, spontaneous ventilation was successfully achieved at plasma concentrations of sufentanil between 0.05 and 0.48 ng ml^{-1}; four patients required naloxone 0.2–0.4 mg to initiate adequate ventilation (plasma concentration of sufentanil: 0.19–0.31 ng ml^{-1}).

$SFC_{P,50}$ for adequate spontaneous ventilation and extubation in the absence of nitrous oxide was 0.25 (SEM 0.03) ng ml^{-1}, γ 5.99 (SEM 3.27).

In patients receiving a variable rate infusion of sufentanil to supplement 66% nitrous oxide, Marty [3] determined the $SFC_{P,50}$ to tracheal intubation as 1.08 ng ml^{-1}; that for adequate spontaneous ventilation after cessation of nitrous oxide was 0.25 ng ml^{-1}. In their patients, individual values of $SFC_{P,50}$:S in the presence of nitrous oxide were in the range 0.2–2.3 ng ml^{-1}. If we base clearance of sufentanil on a mean estimate of 1000 ml min^{-1}, and $SFC_{P,50}$:S as 0.3 ng ml^{-1}, then the average maintenance requirement for sufentanil during nitrous oxide anaesthesia will be about 0.3 μg min^{-1}.

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British Journal of Anaesthesia 1990; **65**: 292–295

CORRESPONDENCE

SUBCUTANEOUS FLUMAZENIL AND RECOVERY FROM MIDAZOLAM

Sir,—The paper by Luger, Morawetz and Mitterschiffthaler [1] makes several points which I think are misleading. It is implied that nausea and vomiting are common side effects following administration of flumazenil. However, flumazenil has no emetic action and nausea and vomiting after its use in surgical patients correlate better with the anaesthetic agents used and the nature of the operation.

Benzodiazepines exhibit antiemetic activity; lorazepam has been shown to be as effective as high dose metoclopramide in the prevention of nausea and vomiting in patients receiving chemotherapy [2]. Where emetic potential is high, as in the period immediately after minor gynaecological surgery [3–5], benzodiazepines may provide some symptomatic relief. All the patients described by Luger's group had undergone such surgery and both fentanyl and halothane were used as part of the anaesthetic regimen. These agents are associated with nausea and vomiting [3, 4]. The postoperative use of flumazenil would be expected to antagonize any protective effect of benzodiazepines on vomiting. Therefore, the complications reported by Luger and colleagues would not seem to be unexpected. Of greater interest is the total absence of nausea and vomiting in the control group. This is surprising, in view of the relatively high incidence of these complications in other similar studies [3–5]. It perhaps says more about the antiemetic potential of midazolam than the shortcomings of flumazenil.

The groups selected for statistical analysis were small and subjective testing provides only a crude index of recovery. Significance testing of such data is thus open to criticism. Analysis of the Choice Reaction Time data shows that there are marked differences in patient performance between group B (flumazenil i.v. and s.c.) and the control group for within patient differences from baseline at both the 5-min and 60-min test points. Furthermore, there is no evidence of resedation in each group using objective criteria alone.

There is no doubt that the action of flumazenil would have been more marked if larger doses had been used. Such doses would have been appropriate given the large quantities of midazolam used. Likewise, problems relating to the confounding influence of the other anaesthetic agents used in this study are not addressed adequately in the discussion of patient recovery profiles. The conclusions drawn by the authors should therefore be modified.

B. Birch
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Sir,—Thank you for the opportunity to reply to the letter from Mr Birch.

It is unlikely that flumazenil has nausea-producing properties [1]. Nevertheless, nausea and vomiting following antagonism of midazolam-induced general anaesthesia using flumazenil have been described as side effects by several authors [2–4]. We agree that after the abrupt antagonism of benzodiazepine-induced anaesthesia, clinically seen as "rapid awakening", nausea might be related to an unmasking effect of the emetic properties of fentanyl and halothane, as described previously [5].

We believe that the incidence of nausea and vomiting in gynaecological patients is related to the residual effects of the anaesthetic agents used and, secondarily, to the nature of the operation. In addition, in our study [6] the emetic potentials of both fentanyl and halothane were intensified by the "body movements during the testing procedures" causing such a high incidence.

The interpretation of our choice reaction time data by Mr Birch is incorrect. The within-patient differences in performance between group B and the control group from baseline at the 60-min test point do not stand careful statistical analysis. The difference between group B and the control group is significant only at the 5-min test point, as noted in our paper [6].

The dose of midazolam given in our study was comparable to that used in previous studies [2, 7, 8]. Likewise, the antagonism of the benzodiazepine effect by the titrated administration of low doses of flumazenil corresponds to recommended clinical practice [2, 7–9]. We are convinced that higher doses of flumazenil might be more effective; however, side effects might become more severe.

The letter of Mr Birch is of interest, but should not detract from our main finding that additional s.c. administration of flumazenil 0.1 mg was not effective in shortening recovery time after midazolam-induced general anaesthesia.

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POWER AND SPINAL ANALGESIA

Sir,—I read with interest the paper by Olsen and colleagues on the effects of spinal analgesia with plain 0.5% bupivacaine administered at spinal interspace L2–3 or L4–5 [1]. However, some of the conclusions that are drawn are not justifiable on the basis of the data presented. Student's *t* test shows that no statistically significant differences can be demonstrated between the groups for the variables examined. This does not imply, however, that there is no clinically important difference between the groups. To interpret these findings correctly, the power of the trial to detect substantial differences must be calculated.

There are several examples where, because of large standard deviations and a relatively small sample size, an unacceptably low probability of detecting major differences exists. A 33% difference between sample means would be a reasonable figure to set as the minimum clinically important difference that one would wish to detect reliably. Using Altman's nomogram [2], to detect a 33% difference for onset time at T12 with a power of 80% and a significance level of 5%, 120 patients would be required. To detect a similar difference for onset time to maximum spread, 70 patients would be necessary. In the first example the probability of a type 2 error is estimated at 65%, in the second at 50%. With the number of patients included in this trial, only a 60% difference in onset time at T12 and a 43% difference in onset time for maximum spread could be detected with adequate power (80%).

When the results of a study are such that it is not possible to demonstrate a statistically significant difference between groups, it is important that the power of the study to detect specified differences between the groups is included. Failure to do this can lead clinicians to assume that no difference exists when a clinically important difference may be present [3].

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Sir,—We thank Dr Trotter for his interest in our work and for giving us the opportunity to comment on the results

The problem put forward by Dr Trotter is by no means new, and applies to all trials with statistically non-significant results. The data presented in our paper permit the reader, like Dr Trotter, to make his own judgement of the power of the study and to relate statistical power and other variables to the clinical situation.

Our results show that no statistically significant differences could be demonstrated in any of the variables measured when a total of 40 patients participated. It is not unlikely that, if 120 patients were included, a statistical significant difference could be shown in one or more of the variables. One important result of our study was that the variation in response was large and, therefore, the exact distribution of anaesthesia in a given patient could not be predicted. It may not be so important that a statistically significant difference of 33% can be demonstrated between the means of 120 patients when the result from patient to patient varies so much. Further research on the subject should focus on a search for these unknown sources of variation.

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ORGANOPHOSPHORUS INSECTICIDE POISONING

Sir,—We read with interest the article by Karalliedde and Senanayake [1] on Organophosphorus Insecticide Poisoning, and in particular the section on the use of atropine to antagonize the muscarinic effects of these agents. Recently we have used a combination of glycopyrrolate and atropine in two cases of organophosphorus poisoning [2]. Glycopyrrolate has pharmacological properties which make it an appropriate adjunct, and at times an alternative, to atropine: it has a high degree of selectivity for peripheral cholinergic sites and has minimal CNS effects because of its quaternary structure [3], making the incidence of central anticholinergic syndrome less likely.

We found that the combination of the two drugs gave adequate control of secretions and bradycardia without causing tachycardia. Glycopyrrolate alone may not adequately control bradycardia or treat asystole [4]. Atropine may also have a role in antagonizing the central effects in this type of poisoning. The authors stated that propranolol may be necessary to correct a severe tachycardia when large doses of atropine are used. We would like to conclude by suggesting that the combination of atropine and glycopyrrolate can provide adequate antimuscarinic effects without the risks of an increased heart rate.

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BLIND NASAL INTUBATION—THE ONLY OPTION?

Sir,—It would be sad if we were to abandon teaching blind nasal intubation, as Dr Williamson rightly protests [1]. The importance of this technique is illustrated by the following brief report.

A bellicose 24-yr-old drug abuser was admitted to hospital for examination of a tender right-sided submandibular swelling. He had no stridor, but speaking and swallowing were difficult and he drooled saliva continuously. Mouth opening was restricted to 2 cm. Following administration of midazolam and pethidine i.v., and cocaine to the nasal passages, an intubating fibrescope was passed gently into the nasopharynx. Preparation to guide the scope under direct vision beyond the nasopharynx was terminated abruptly by pain.

Thirty minutes later, after the promise of a general anaesthetic, the patient was positioned in the right lateral and slightly head-down position. Inhalation anaesthesia was induced with halothane in oxygen via a Magill attachment. Attempts to pass an uncuffed 7.0-mm red rubber nasal tube into the right postnasal space were accompanied by vocalization, tachycardia and hypertension. Anaesthesia was therefore continued using the left nasal passage, aided by administration of 25-mg boluses i.v. of propofol (to a total of 125 mg). Further increase in depth of anaesthesia was accompanied by airway obstruction and only some positions of the tube produced a clear airway.

Tracheal intubation was surprisingly easy and required only slight manoeuvring and rotation of the tube. Examination then revealed a plum-sized indurated swelling causing marked deviation of the uvula and soft palate to the left. There was no room for a throat pack, but an air-tight seal was achieved by the simple expedient of removing the mouth gag and allowing the jaw to fall. The surgeon proceeded directly to a tracheotomy before eventually locating, extraorally, 10 ml of foul-smelling pus deep to the right medial pterygoid muscle. Anaesthesia was concluded uneventfully.

Patient co-operation is vital for the success of awake fibreoptic intubation. The exquisite tenderness at the initial attempt in this patient was sufficient indication that fibreoptic intubation under local anaesthesia was doomed to failure. Had the correct nasal passage (aided, for example, by a CT scan) been selected in the first instance, similar tenderness with withdrawal of co-operation was inevitable, as proved subsequently by the extent of the inflammatory process.

The main advantage of blind nasal over fibreoptic intubation in such a situation is the facility continuously to maintain and assess the airway while inducing anaesthesia with an FI_{O_2} approaching 1.0. If airway obstruction occurs, restoration by minitracheostomy or jet ventilation via a cricothyrotomy is safer and simpler when the patient is oxygenated and asleep.

D. Suresh
London

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SPINAL OBSTETRIC ANAESTHESIA WITH A 29-GAUGE NEEDLE

Sir,—Reports of the use of spinal anaesthesia for general and orthopaedic surgery in young patients using the 29-gauge spinal needle—that by Dahl and colleagues [1] is the most recent—indicate a low incidence of post-dural puncture headache (PDPH) [2, 3]. As far as we know, there is no information in the anaesthetic literature on its incidence in obstetrics.

We have used an 8-cm, 29-gauge spinal needle with a 23-gauge introducer (Vygon) for elective lower segment Caesarean section (LSCS) in 61 patients, following a standard procedure for spinal anaesthesia. The onset of block was rapid enough (5–7 min to the 7th–8th thoracic dermatomes) to justify the spinal route for emergency LSCS in seven patients. Despite a policy of early ambulation (within 24 h) and a population especially at risk, the incidence of PDPH was zero.

There is a "learning curve" in developing the skill to manipulate so fragile a needle [Tunstall ME, personal communication]. On three occasions we resorted to extradural anaesthesia because we could not aspirate cerebrospinal fluid from the subarachnoid space. Other practical difficulties described well by Dahl [1] were overcome by the extradural–spinal technique. Currently, we are assessing a prototype 10-cm, 29-gauge spinal needle with a Luer fitting (Steriseal) passed through an *in situ* 8-cm, 16-gauge Tuohy extradural needle (Steriseal). The Tuohy needle helps to direct the crucial last millimetres transit of the spinal needle. If spinal anaesthesia proves occasionally to be inadequate, the combined technique should permit the ready substitution of extradural anaesthesia.

Our results suggest that the use of a 29-gauge needle for spinal anaesthesia in operative obstetrics deserves further study.

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P. V. SCOTT
C. A. PINNOCK
Redditch

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EMLA: COMPLICATIONS

Sir,—I was interested to read the letter from Norman and Jones reporting complications with the use of EMLA [1]. Recently, an 8-yr-old boy weighing 25 kg presented for squint surgery. He had a mild history of asthma, not requiring medication, and was otherwise fit. Premedication was with trimeprazine 3 mg kg^{-1} and atropine 1 mg given orally, and EMLA cream was applied to the dorsum of both hands. According to his mother, a trained nurse, he became somewhat disorientated after about 20 min, pulled off the plastic dressing and licked the EMLA off the back of one hand. Within minutes he blacked out for about 10–15 s, then recovered without any apparent ill-effect. There were no seizures. Unfortunately, the story is uncorroborated as no ward staff witnessed the event. All subsequent clinical observations were normal.

Seizures following ingestion of viscous lignocaine have been reported in children [2, 3], and it has been recommended that the total single dose should not exceed 5 mg kg^{-1}. In this instance, approximately one 5-g tube was ingested, equivalent to lignocaine 125 mg and prilocaine 125 mg. If this had been swallowed, it is unlikely that toxic blood concentrations (5–10 μg ml^{-1}) would have been achieved, as first-pass metabolism in the liver results in about 35% bioavailability. It is possible, however, that there was rapid absorption of lignocaine from the oral mucosa, producing a blood concentration sufficient to cause transient bradycardia or other disturbance of rhythm. There may be other theories, but it would seem prudent to take steps to prevent small children removing the adhesive dressing that is applied over EMLA.

I. G. JAMES
London

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AN INTERNATIONAL CONSENSUS ON MONITORING

Sir,—The Board of Faculty of Anaesthetists, Royal Australasian College of Surgeons were interested to read the recent Editorial [1]. We were dismayed to note that there was no reference to our Policy Document P18 (1988) on Monitoring for Anaesthesia, and therefore the views of the Australian standards were incomplete. The Faculty standard is that all recommendations in the document needed to be in place by January 1, 1990, and in particular that there should be:

(1) An oxygen supply failure alarm fitted to the anaesthetic machine.
(2) An oxygen analyser in continuous operation.
(3) A pulse oximeter exclusively available for each anaesthetized patient.
(4) A disconnect alarm in continuous operation when an automatic ventilator is in use.
(5) An electrocardiograph, temperature monitor, and carbon dioxide monitor available for every anaesthetic patient.
(6) A neuromuscular function monitor available where clinically indicated.

The Faculty is currently revising this Policy Document and it is highly likely that the new Policy will require increased monitoring standards, particularly for capnography.

The Board of Faculty would endorse the Editorial comments on ergonomic considerations which must be taken into account when considering patient safety. Distraction by monitors must not be permitted to interfere with the proper observation and management of the anaesthetized patient.

A. B. BAKER
R.A.C.S., Melbourne

REFERENCE

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Sir,—We are sorry that we failed to include the important initiative of the Faculty of Anaesthetists of the Royal Australasian College of Surgeons and we are grateful to Professor Baker for highlighting the main recommendations.

A. A. SPENCE
A. WINTER
Edinburgh

British Journal of Anaesthesia 1990; 65: 296–300

BOOK REVIEWS

Techniques of Regional Anaesthesia, 1st Edn. By D. B. Scott, Published by Appleton & Lange/Mediglobe, Connecticut, California, Switzerland. Pp. 224; indexed; illustrated. Price £69.00.

Introduction to Regional Anaesthesia, 1st Edn. By D. B. Scott. Published by Appleton & Lange/Mediglobe, Connecticut, California, Switzerland, Pp. 96; indexed; illustrated. Price £19.95.

These two monographs have been written by a well-known authority on local anaesthesia, Dr Bruce Scott, who is currently an employee of Astra Pharmaceuticals Limited and was previously a consultant anaesthetist and senior lecturer in the University of Edinburgh.

Introduction to Regional Anaesthesia is the offspring of *Techniques of Regional Anaesthesia*. It contains approximately 30% of the information contained in the parent book and concentrates on methods and techniques appropriate for the trainee anaesthetist. It is illustrated lavishly and reproduces many of the coloured diagrams from its parent; it is clearly appropriate only for the trainee physician anaesthetist, and it can fit into the traditional "white coat" pocket.

The parent text, *Techniques of Regional Anaesthesia*, is the successor to "*Illustrated Handbook in Local Anaesthesia*" edited by E. Eriksson. The first edition of this text could be obtained free of charge from the Pharmaceutical industry and I well recall that, when I was a trainee, it was the ambition of all junior anaesthetists to solicit a copy from the local pharmaceutical representative while stocks remained. Unfortunately, I "lost" my copy of the first edition and such was the demand that I had to wait until the second edition was published in 1979 for a replacement, but by this time the sum of £15.00 was being charged. *Techniques of Regional Anaesthesia* is a worthy successor to Eriksson's popular book, but the cost has now escalated to £69.00, a price greater than some well-known large introductory texts of anaesthesia.

Techniques of Regional Anaesthesia reproduces many of the excellent coloured illustrations from Eriksson's text but, in addition, there are new diagrams drawn by Paul Buckhoj and additional photographs and radiographs have been obtained from other sources. The text is obviously designed for a worldwide audience and, in order to produce a single type setting, the World Health Organisation's International Nonproprietary Name Convention has been used for drug names. These tend to follow the U.S. pattern, for example lidocaine, epinephrine, tetracaine.

In common with those of its predecessors, the contents comprise an introduction on preoperative assessment and management, mode of action and complications of regional anaesthesia. The reader is then taken step-by-step through the practical performance of the majority of local anaesthetic blocks in use. Whereas previous editions of Eriksson were multi-authored, Dr Scott indicates that he has obtained help and advice from colleagues where the block did not fall within his own personal experience. Many blocks described, for example coeliac plexus block and trigeminal nerve block, may be confined to those practising in chronic pain clinics; here, some readers may feel that the description is inadequate for the performance of such specialist techniques. However, for the more commonly used blocks, in general the descriptions and illustrations provide clear, simple and precise anatomical guidance. Some new blocks, not found in previous editions, have been included; for example, interpleural injection, which is described as being easy to perform and devoid of many side-effects, with pneumothorax occurring only rarely; one hopes that this rather optimistic description does not encourage the widespread use of a so far unproven technique.

Since the publication of the first edition of Eriksson, many other textbooks of practical, regional anaesthesia have appeared, some illustrated liberally in colour. However, *Techniques of Regional Anaesthesia* follows the tradition of its predecessors in setting the standard by which all other similar texts are judged. The diagrams and illustrations by Buckhoj are, simply, quite superb and the text is lucid, well-written and concise.

G. Smith

Metabolic Response to Surgery. Baillière's Clinical Anesthesiology. International Practice and Research, Vol. 3, No. 2. Edited by D. R. Bevan. Published by Ballière Tindall, London. Pp. 155; indexed. Price £18.50.

It is perhaps highly appropriate that a book of this title should appear in the year of the death of Sir David Cuthbertson, the father of this subject. It is also perhaps a pity that it should take such a limited view, particularly when compared with the other books that have appeared on the subject in the past 5 years. This slim volume could better have been entitled "some aspects of the metabolic response to surgery." However, when a volume appears as part of a series there must inevitably be restrictions on size and space.

Dr Bevan has edited a book of essentially nine chapters, all concentrating on specific aspects of metabolic physiology and all written by authorities in their own field—Kehlet on modifications of metabolic responses by regional anaesthesia, Hall on modifications by general anaesthesia and opioids, Carli on metabolic disturbances of hypothermia, *etc*. Philbin writes on antidiuretic hormone and Harry Shizgal writes an introductory chapter purportedly reviewing the whole subject, but perhaps inevitably giving the main emphasis to his interest in body composition. There is a chapter also on liver failure which seems strangely out of place as it concentrates almost entirely on hepatic disease and the processes of transplantation, rather than the liver's role in the body's response to a traumatic or septic insult.

I found the whole book rather unsatisfactory. Each chapter in itself is an excellent review of its subject, but it was really only in the final chapter from Askanazi's group that one felt that any effort was being made to pull the whole subject together. That chapter was entitled "Metabolism in the Intensive Care Unit," but the work reviewed was drawn largely from surgical patients or those suffering discrete sepsis rather than the problems of multiple organ failure.

These criticisms, however, are probably more a reflection of the subject itself and editorial limitations than of the way the book has been written. I can strongly recommend the volume to anyone who is interested in the subject as an excellent review of certain aspects; but a comprehensive treatise it is not.

I. T. Campbell

Problems in Anaesthesia, Analysis and Management. Edited by S. Feldman, W. Harrop-Griffiths and N. Hirsch. Published (1989) by Heinemann Medical Books, New York. Pp. 180; indexed; illustrated. Price £12.95.

This little book is divided into four sections of approximately equal length. The first two sections deal with cardiovascular and airway problems. The classification of Sections 3 and 4 is less well organized and includes a *pot-pourri* of problems ranging from (in Section 3) haematuria to convulsions and (in Section 4) from failure to recover consciousness to inadvertent subcutaneous injection of drugs. We do not criticize the list of problems considered, but the arrangement in four sections seems to be unnecessary.

The index to this little book is comprehensive and facilitates its use. Many of the problems described are, unfortunately, not infrequent. They do, however, pose a frightening prospect for inexperienced anaesthetists who are, of course, the target audience. It is clear from the detail in the sections that the authors have great experience. They have included tables and diagrams which complement the text. The sections devoted to problems arising with the airways and the cardiovascular system are particularly good examples.

There are a few glaring omissions, such as the absence of the mention of tachycardia when bleeding occurs in the presence of a beta-blocker. However, although it is only a small book, its contents will give the reader enough food for fear!

This little book will be extremely helpful to all those in their early stages of training and, in particular, in preparation for the Part 1 examination for the Fellowship of the College of Anaesthetists. We would recommend that all trainees read it and continue to take care.

N. Un and T. E. J. Healy

Safety and Cost Containment in Anesthesia. Edited by J. S. Gravenstein and J. F. Holzer. Published by Butterworths, London. Pp. 257; indexed. Price £22.95.

Throughout the past 150 years, anaesthesia morbidity and mortality rates have declined despite growing surgical sophistication, more operations being performed especially at the extreme ages of life, and more patients presenting as critically ill. Indeed, anaesthetists have repeatedly evaluated the nature of risks in anaesthesia and have made efforts to reduce them. The specialty is considered by many to be the leader in medical risk management and patient safety. This position has been attained by attention to several factors which include: early measurement of risks, provision of postgraduate courses and meetings, institution and inspection of comprehensive training programmes, and development of new technology.

This is a superb book, which could not have been published at a better time, especially as the medical profession in the U.K. is now grappling with the spectre of resource management, proposed changes in practice and funding of services, introduction of audit and peer review, and the bogey of massive medico-legal premiums and malpractice settlement costs. It is one of the most important books to be published in the specialty of anaesthesia for some years. The subject is, of course, safety and the costs of anaesthesia care, and how the two relate. There are 25 contributing authors ranging from senior anaesthetists to experts on purchasing, risk management, lawyers, major equipment manufacturers and suppliers, and experts from various other walks of life. There is virtually no overlap or inconsistency and although it is true that all the contributors hail from the U.S.A., this does not present any problems as adequate considerations of European studies are included. Each contributor has provided a thoughtful, readable and comprehensive input which makes very good sense. The book is well referenced throughout and contains both an author and a subject index.

This book represents excellent value for money and is essential reading for all anaesthetists, and health care professionals involved with the specialty. Nowhere else are all the relevant topics gathered together so comprehensively and yet so succinctly; the book contains a tremendous amount of information in addition to giving plenty of food for thought about the future of our specialty.

A. P. Adams

Update in Intensive Care and Emergency Medicine, Volume 9: Brain Failure. Edited by D. Bihari and J. W. Holaday. Published (1989) by Springer Verlag, Berlin. Pp. 275; indexed; illustrated.

This book is a synopsis of the proceedings of a research conference entitled "Brain Failure", organized by the European Society of Intensive Care Medicine in conjunction with the Society of Critical Care Medicine in Brussels in March 1989. The stimulus for this meeting was the frequent presence of central nervous system (CNS) dysfunction in a variety of widely different clinical conditions. The conference aims were to outline and discuss the results of current research into various aspects of brain failure that may arise in the intensive care unit. Participants were from Australia, U.S.A. and Western Europe, had diverse backgrounds and included specialists in Anaesthesia, Immunology, Intensive Care, Medicine, Neurology, Neuropsychiatry, Neurosurgery, Pharmacology and Physiology.

The book comprises 20 chapters, each with a comprehensive reference list, covering a diverse range of topics including a fascinating section on the effects of brain failure on immunocompetence, current understanding of the pathobiology of CNS trauma and ischaemia with reference to potential avenues for therapy, the pathophysiology of encephalopathies, the use of dual oximetry for management of brain failure, an excellent chapter on the appropriate use of evoked potentials for monitoring different CNS disorders, recent trends in the management of neurosurgical conditions and methods of predicting outcome in patients with brain failure.

Chapters are written with different styles and while some give a comprehensive review of a topic, others concentrate on areas of primary interest to the author. This reduces the value of this book for the anaesthetist in training, although appropriate background reading is provided in the reference list at the end of each chapter. However, the book is to be recommended to all doctors involved in critical care medicine, and especially to those involved in CNS research.

My main criticism relates to the quality of editing and printing. There are numerous typescript errors, giving the impression that preparation was rushed. In one chapter, figure numbers do not correctly correspond with references in the text and there is marked inconsistency between text and figure legends.

I believe the book could have been improved by the inclusion of a section on the use of transcranial Doppler ultrasound in patients with brain failure, and a chapter on appropriate administration of anaesthesia to patients with brain failure.

In summary, this is an interesting book containing information from many disciplines and providing the reader with an update of current trends in CNS research. It is flawed by poor editing and will probably be of more interest to intensivists, especially those involved in brain research, than to the anaesthetist in training.

N. M. Deardon

Cardiopulmonary Resuscitation, 1st Edn. Edited by W. Kaye and N. G. Bircher. Published by Churchill Livingstone, New York. Pp. 231; indexed; illustrated. Price £30.

This multi-author book examines several critical aspects of the practice of cardiopulmonary resuscitation (CPR) as seen through the eyes of several distinguished authorities.

There is a valuable chapter on the history of both early and modern resuscitation by Peter Safar, who has collected a wealth of archival material with nearly 300 references and photographs of early pioneers who are household names to students of CPR.

The reader who is looking for detailed clinical guidance may be somewhat disappointed in the extent to which this aspect is covered. Nicholas Bircher has written two good chapters on the physiology and pharmacology of CPR and the problems occurring after resuscitation, and there is good therapeutic information contained in the contribution by Charles Schleien and Mark Rogers on CPR in infants and children. However, the two-page offering covering resuscitation after near drowning, trauma, electrocution and hypothermia is poor.

Balancing this deficit are good chapters relating to the organization and priorities for resuscitation services both inside and outside hospital. Richard Cummins and Judith Graves from Seattle/King Country, Washington produce good data in favour of immediate bystander CPR backed up by rapid defibrillation which results in a 32% survival rate. If the bystander does not react smartly or if the professional services cannot respond within a few minutes, survival rates decrease catastrophically.

Paul Rogers and Ake Grenvik have written a chapter on Foregoing CPR which should be read and acted upon by all responsible for hospital CPR services so that patients with no hope of a meaningful recovery are not subjected to undignified and unnecessary resuscitation attempts.

Bill Kaye and his colleagues have produced an excellent section on educational aspects which will be most valuable for CPR instructors in the U.K., as it contains not only training guidelines, but also evaluation procedures. The academic alternatives to standard methods of CPR are reviewed well by James Niemann. These contribute to our understanding of resuscitation requirements and techniques, but it is noted wisely that they are not appropriate for application in current clinical practice.

The chapter on perioperative CPR by Jean Lumley and David Zideman concentrates, in large part, on prevention and causes, with a small section on immediate treatment. An action plan for cardiac arrest occurring during anaesthesia would have been a useful addition. There is little mention of the later treatment in the intensive care unit.

All in all, this is an extensively referenced (although few from outside North America), interesting book to give food for thought for those responsible for the organization of and training for resuscitation. It is not the traditional clinical textbook.

P. J. F. Baskett

Sepsis—An Interdisciplinary Challenge, 1st Edn. Edited by K. Reinhart and K. Eyrich. Published by Springer-Verlag, Berlin, Heidelberg. Pp. 391; indexed Price DM 173.60.

This book is a collection of 31 papers presented originally at the 2nd International Steglitz Symposium held in Berlin in October, 1987. It explores the aetiology, prevention and treatment of sepsis from both pure science and clinical aspects.

The first four chapters examine the epidemiology and pathophysiology of sepsis and septic shock. Chapter five reviews the new methods in microbiological diagnosis, in particular the newer blood culture systems. The radiometric Bactec system has been utilized widely in the U.K., but is now being superseded by a newer non-radiometric system which removes some of the difficulties of storage and disposal of radioactive material. A system not mentioned is the Signal bottle, which detects organisms by production of gas which displaces broth into an indicator device, thereby removing the need for expensive reading equipment. Antigen detection methods are considered, but I was surprised to read that some of these (co-agglutination, latex agglutination and counter-immune electrophoresis) are more sensitive than a Gram-stained smear. Most studies have confirmed the useful specificity of these techniques, but find them of equal or lesser sensitivity than Gram stains.

The next paper identifies the symptoms and signs which may allow early diagnosis of sepsis and advances clinical and laboratory criteria which will confirm the diagnosis. The paper on useful and useless measures to prevent infection on intensive care units is essential reading for all those who care for patients in such units. This is an area where traditional practices such as floor disinfection and wearing of overshoes have been appraised scientifically and found to be worthless. The great importance of meticulous hand hygiene is stressed again, as is the need for an effective infection control team and a judicious antibiotic policy. Isolation of patients in the ITU may be difficult with regard to staffing and intensive patient care, but its role (both in protective and reverse barrier mode) is emphasized. Another important point is the value of regular blood cultures in patients with suspected sepsis in the ITU.

Following papers examine the therapy of acute respiratory distress syndrome and the controversial role of steroids in sepsis management. The centre section of the book focuses on the physiological changes in sepsis, with regard to changes in the cardiovascular, respiratory and other organ systems. The immunological consequences of sepsis are also covered in detail, with current and future therapeutic applications considered, including data on high-titre antiserum in Gram-negative endotoxic shock. I found the paper on antimicrobial therapy rather vague in its recommendations, and this would need to be augmented by local prescribing policies.

I would commend this collection to those concerned with patient care in the ITU as a useful review on the prevention and management of sepsis. Understandably, it is written from a largely German perspective, but each paper is well-referenced from the international literature. Nonetheless, those with less interest in the pathophysiology of sepsis will find useful clinically-orientated updates on patient management.

R. A. Swann

Anesthesia and Uncommon Diseases, 3rd Edn. Edited by J. Katz, J. Benumof and L. Kadis. Published by W. B. Saunders Co., Philadelphia. Pp. 964; indexed; illustrated. Price £53.50.

Many anaesthetists will have awaited, with anticipation, the appearance of the third edition of this classic reference book. There are now 30 contributors, and a change of authors has occurred in almost 50% of the 20 chapters. Anaesthesia for eyes and ENT surgery and a section on liver diseases are new additions. The trauma chapter has been expanded to include burns.

Almost inevitably, chapters in a multi-author text book tend to be uneven in approach and quality. Successive editions of this book have largely eliminated the former problems, but variations in quality remain. Updating of an existing text may be particularly difficult, especially if no dramatic advances have occurred in a subject. However, the reader must be convinced that the author has not only kept abreast of the literature, but speaks as a practising anaesthetist. Many chapters have succeeded in this respect, some having undergone complete revision, but a few have not.

Some contributions are outstanding and, as the editors suggest, "will become recognised as the definitive treatise for the subject matter presented". The chapter on muscle disease has been substantially updated, with particularly well written sections on muscle dystrophies and malignant hyperthermia. New topics include neuroleptic malignant syndrome, drug-induced myopathies and trismus. The chapter on genetic disorders is excellent and has doubled in size. Rather quaintly, concealed within it, are noteworthy sections on anaesthesia for extracorporeal lithotripsy, liver transplantation, hypoglycaemia, seizure disorders and evaluation of coronary artery disease. I approached the chapter on geriatric anaesthesia with some foreboding, but was delighted to find that the new author has contributed a lively and interesting account of the topic. One criticism applicable even to the best written chapters, is that there may be excessive pathophysiological detail. It is thus often difficult to sift out essential anaesthetic information rapidly.

Some chapters are disappointing. That on disorders of pregnancy contains only 15 references which are less than 10 years old. These relate mostly to potential teratogenic drugs and side effects of beta stimulants used for suppression of premature labour. That on gastrointestinal disease has undergone reorganization but, similarly, little update. The first section presents new work on gut motility and secretions, but that on specific disorders is virtually unchanged and contains no references within the past 10 years. While admittedly the concept of many gastrointestinal diseases is unaltered, there have been advances. References to new work on the pathophysiology and management of carcinoid syndrome is conspicuously absent.

The chapter on renal disease fell below my expectations. Detailed sections on the pathological and medical aspects of individual renal diseases seem to have taken precedence over practical and essential anaesthetic management. There is a page on the technicalities of renal dialysis, but nothing on the real practical anaesthetic problems posed by dialysis patients. More specifically, it was surprising to find no mention of hepatitis B, erythropoietin, uraemic encephalopathy, cardiovascular lesions, the problems of venous access and protection of the arteriovenous shunt. The selection in the chapter on infectious diseases is still oddly limited, being mainly concerned with septic shock and AIDS.

Inevitably, overlap occurs between chapters. Detailed accounts of glycogen storage diseases appear in the chapters on both genetic disorders and muscle diseases. Specific conditions associated with eye and ENT disease are dealt with more fully in other chapters. Spinal cord injury has been duplicated, but the more detailed account of the two appears in the neurological section.

The presentation of the new edition has improved. Headings are clearer and the lists of chapter contents have been expanded. The format of the references within the text is now almost uniform. It is, indeed, this plethora of references which is one of the merits of the book. In some cases, however, the references are quite antique and judicious pruning should have been carried out. Two chapters have only 12% of their references published within the past 10 years, in contrast with over 80% in two other chapters. Certainly, some diseases have changed little, but it is still depressing to be referred to a review of a topic written more than 30 years ago!

Overall, this remains an excellent reference book. As a hardback it is unusually good value for money. It certainly should be available in every department of anaesthesia, and I think that a number of senior anaesthetists will wish for personal copies.

R. A. Mason

Clinical Monitoring, 1st Edn. Edited by C. L. Lake. Published by W. B. Saunders Co., London. Pp. 832; indexed; illustrated. Price £67.85.

During the past decade there has been a remarkable growth in the use of monitoring in the operating theatre and intensive care unit. There are two international journals devoted to the subject and now there is a second major textbook on the use of monitoring in clinical practice. The first major text, *Monitoring in Anesthesia and Critical Care Medicine*, was edited by Casey D. Blitt and appeared in 1985. A second edition has just been published (1990). *Clinical Monitoring*, edited by Carol L. Lake, Professor of Anesthesiology, University of Virginia Health Sciences Centre, is somewhat shorter but as it is aimed at a similar audience, comparisons are inevitable.

In the second edition of the Blitt text, approximately 350 pages are devoted to the cardiovascular system, 100 to the respiratory system, 120 to the central nervous system, 130 to miscellaneous topics and 140 pages to the particular requirements of the subspecialties. Lake devotes approximately 250 pages to the cardiovascular system, 60 to the respiratory system and then has approximately 300 pages dealing with obstetrics, computerized monitoring, the anaesthetic machine and other miscellaneous topics, followed by 150 pages on the central and peripheral nervous system. The sequence of chapters seems less logical than that adopted by Blitt.

When analysing the text one must consider how the authors deal with the three problems in monitoring, namely: the acquisition of the signal, the processing and display of the data and the interpretation of the measurement. Lake commences with two excellent chapters on ECG monitoring for ischaemia and for disturbances of heart rhythm. The advantages and disadvantages of the various leads are clearly discussed, the sources of artefact are listed, and the common perioperative arrhythmias are well illustrated. These chapters are followed by others on intravascular pressure measurements, with brief synopses of the relevant physiology to aid interpretation. The remaining chapters in the cardiovascular section are clearly written, comprehensive reviews on intraoperative echocardiography (with superb coloured plates) and the monitoring of ventricular function.

Section two, on the monitoring of respiratory function, is very disappointing. There is no mention of methods of measurement of carbon dioxide production, oxygen consumption, or the assessment of adequate ventilation and there is only a very brief description of devices used to measure tidal volume either directly or indirectly. The later sections on gas analysis do not mention the development of rapid paramagnetic oxygen analysers which have revolutionized oxygen monitoring and, with the exception of the mass spectrometer, the only other techniques for vapour analysis listed are Raman scattering and piezo-electric detectors. The infra-red analyser does not even appear in the index!

Section three deals with maternal–fetal monitoring in obstetrics. This has a good introductory section on the changes in maternal physiology during pregnancy and provides comprehensive coverage of the problems of monitoring during labour. There are particularly good sections on the problems associated with pre-eclampsia and cardiac disease. The later sections deal with the use of computers in anaesthesia, patient data management systems and monitoring the anaesthetic machine. There is a detailed chapter on intraoperative evaluation of haemostasis and a particularly well-written chapter on perioperative biochemical monitors which defines the type of sample required, the method of analysis, the reference ranges, the sources of inaccuracy and the physiological role of the measurement.

The final section of the book deals with intracranial pressure measurement, the EEG, monitoring the neuromuscular junction and evoked potentials. These chapters are fairly comprehensive reviews of the current state of the art, but the relevance of the EEG and evoked potentials to the assessment of "depth of anaesthesia" is not discussed critically.

Both volumes provide a comprehensive review of the subject of monitoring. They are fully referenced and inevitably include a great deal of physiology and pharmacology related to anaesthesia. As would be expected with multi-author texts, there is a variation in standards between sections. Blitt has good introductory chapters dealing with the philosophy of monitoring and the use of the senses, whilst Lake's introduction is somewhat disjointed with sections on history, the Harvard standards and electrical safety. Blitt's layout is logical and comprehensive, but there is some repetition in the chapters dealing with monitoring in the subspecialties. Lake has some excellent sections at the beginning and the end, but is weak in some areas.

The choice must ultimately be a personal one, though the price will deter the personal purchaser. If forced to make a choice for my departmental library, I think I would spend the extra £7.50 for the second edition of Blitt, for the latter has a more logical layout, a panel of distinguished authors who maintain a consistently high standard and, to my mind, write with more clinical relevance than some of those in the book edited by Lake. However, any Department fortunate enough to possess either of these volumes would have a wonderful resource which could provide many hours of fascinating education over the whole spectrum of anaesthesia and critical care.

M. K. Sykes

"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL

THE ANIMALS (SCIENTIFIC PROCEDURES) ACT 1986 AND RESEARCH INTO ANAESTHESIA

The Animals (Scientific Procedures) Act 1986 came into force on January 1, 1987 and licensed all research in the U.K. on *living vertebrates which might have the effect of causing that animal pain, suffering, distress or lasting harm.* The Act was the culmination of many years of debate and activity by the anti-vivisectionist movement, but perhaps more importantly, by moderate welfare organizations such as The Committee for the Reform of Animal Experimentation (a grouping of moderate animal welfare organizations), the Royal Society for the Prevention of Cruelty to Animals, the British Veterinary Association and Fund for the Replacement of Animals in Medical Experiments. There had also been increasing public concern over the use of animals [1]. Whilst the old 1876 Cruelty to Animals Act had worked well, it had not kept up to date with current ethical thinking (consider for a moment our use of animals in the nineteenth century and now) and its wording and original concepts were clearly dated. For example, although the Home Office Inspectorate in practice had been interpreting the words in the 1876 Act "calculated to give pain" to include other aspects of potential "suffering" in experimental work, it did not refer overtly to distress, discomfort, fear etc.; nor did it effectively limit any such adverse effects (unless the pain was sufficient to be classified as severe and enduring). Moreover, the old Act did not take into account the objectives of the research, or the provenance of animals (the public believed—and some still do—that pet cats and dogs are used in research). In addition, it did not apply to those animals used in potentially severe non-experimental (*sic*) procedures, for example tumour and parasite passage, raising antisera. Today, under the new 1986 Act, the purpose of the research is considered when granting a licence, the supply of animals is controlled carefully and licensed, and all *scientific procedures* are covered, not simply those deemed to be an "experiment"—that is, that by definition had an unknown outcome.

Before any animal research may be carried out, three types of licence are needed. The first is a **Certificate of Designation** which approves the Establishment's facilities for keeping, or for breeding and supplying experimental animals. This places a fairly heavy responsibility on a senior person in the designated establishment (such as the Vice-Chancellor or Registrar in a University, or a board member in a commercial company) to provide and maintain adequate staffing and facilities, and to ensure the main provisions of the Act are observed by members of the institution. The certificate holder has to appoint two named persons: a veterinary surgeon, and a person in day-to-day care of the animals. These named persons have a statutory responsibility to take remedial action whenever the health or welfare of an animal gives rise to concern—whether it is a stock or experimental animal.

The second type of licence is a **Project Licence** which licenses a programme of research work. This is the most effective part of the new Act, as it aims to ensure good laboratory animal science—ensuring the science is soundly based and that the animals do not suffer unnecessarily or unwittingly. The application for a project licence has to provide details of the background to the research, the broad objectives, the number of animals to be used, and the potential benefit (a gain in fundamental knowledge is acceptable, in addition to applied research directed towards some human or animal disease or hazard). Details of the research programme, as one might draw up for an Ethics Committee or grant application, must be given and the applicant also must testify there are no *in vitro* or *ex vivo* alternatives to using living animals. All animals to be used on the project must have come from registered Breeders or Suppliers (unless the animals are not on Schedule 2, for example farm species, or a specific exception has been approved) and this may increase the price of some species, for example dogs. At the end of every year the project licence holder has to inform the Home Office of the number of animals used under the licence.

Perhaps the most interesting part of the project licence is the classification of the *predicted adverse effects* on the animal (termed "severity") as mild, moderate and substantial—but how does one measure and grade these adverse effects? (There is also a fourth grade, as there is a termination condition attached to every Personal Licence (see below) and "severe pain or *severe distress*" will not be permitted—and therefore has to be recognized.) These adverse effects are then balanced against the *potential benefits* from the research—in a type of cost–benefit analysis. In practice, a recommendation is made by the Home Office Inspector on behalf of the Secretary of State. The moral principle is obvious and laudable, as nobody would wish to see an animal suffer for trivial gain, and most would find it acceptable that mild pain or discomfort could be caused to relieve human suffering—it is the area in between that may be difficult to judge and gain a consensus [2]. In practice, the mere fact that scientists have been asked to specify the likely adverse effects and their incidence, and then to detail how these adverse effects will be mitigated has highlighted the wellbeing of the animals and also, therefore, the dilemmas. Scientists, by and large, endorse the concept and it behoves them to consider their personal ethical stance before embarking on any animal research; they may even be reassured by such an analysis. A moment's thought will show that good animal welfare and a reduction in suffering will, more often than not, lead to better science, as pain and distress are usually unwanted side effects in experimental work (e.g. a kidney transplant) and lead to unnecessary suffering and reduced scientific accuracy.

What might be of interest to anaesthetists is how one can recognize pain, distress and discomfort in animals, and how it can be relieved [3]. There are analogies between animals and babies/children in their lack of verbal communication, but then "they cannot mislead you either". There is a further complication as there are few licensed analgesic and anxiolytic drugs in the U.K. for many laboratory animal species (ironically, as such drugs almost certainly will have been researched, developed and safety tested using them). In essence, measuring these adverse effects becomes an assessment of deviation from normality and this requires considerable expertise when one considers the many species and strains (breeds), and the varied physiological, psychological and behavioural patterns that can be exhibited, even in their restricted environment. Here advice from animal technicians, the named veterinary surgeon and the named person in day-to-day care becomes invaluable. One anomaly is the public's (misguided?) concern for dogs, cats, horses and primates, resulting in special justification having to be given for the use of those species. However, the evidence for pigs or rats "suffering" less than dogs or cats is highly debatable—such is the public's logic and morality!

The third type of licence is a **Personal Licence**—in effect, a certificate of competence to carry out a regulated procedure on an animal—that is, any scientific technique which may have the effect of causing pain, suffering, distress or lasting harm; even taking a blood sample will require a licence. The licence details each technique by species and whether an anaesthetic is required. All new licensees (regardless of whether they have a medical or veterinary training) must be supervised for their first year (or until their supervisor considers them competent, when an application can be made to the local Home Office Inspector to remove the restriction). No one may carry out any research even with a personal licence unless they are covered by a project licence and for the first year applicants have to specify the project licence under which they wish to work. Giving an anaesthetic or analgesic is considered as having the potential to cause animal suffering and so requires both project and personal licences. A new applicant requires a sponsor who will testify that (s)he has the necessary background knowledge, has practised where appropriate on dead animals, and is of a suitable character. The sponsor and supervisor are normally senior licensees and may be the same person. Training in scientific techniques can thus be phased, culminating in direct assistance on living animals when the licence has been granted. It is not permitted to use animals for the purposes of demonstrating or for gaining manual skills. Some 25 conditions are attached to a personal licence which, by and large, are common sense but should be read carefully. (Eleven are considered serious offences and a breach may result in a gaol sentence of up to 3 years or a large fine; the other 14 are less serious and may incur suspension or revocation of the licence, or a shorter holiday at Her Majesty's pleasure.)

Euthanasia is also controlled under the 1986 Act and Schedule 1 lists those methods that are permitted without the authority of a personal licence, are relatively easy to carry out (do not require special skills or strength), and which leave minimum room for misuse. Other methods can be used, but they have to be justified and licensed.

Neuromuscular blocking agents may be used, but are of obvious concern and their use is tightly controlled. The use of a neuromuscular blocking agent in place of an anaesthetic, or their use without the authority of a personal licence, are considered serious offences; the Home Office Inspector has also to be given 48 h notice of intended use. The Home Office and the Physiological Society have produced excellent guidelines on the use of muscle relaxants, and they perhaps raise a few points worthy of consideration in human clinical practice.

Reuse of animals is permissible, but is carefully controlled through the "donor" and "recipient" Project Licences and should be discussed with the Home Office Inspector.

In conclusion, the 1986 Animals (Scientific) Procedures Act seems to be working well to the benefit of science and animals. Its major provisions inevitably mean more paperwork and outside scrutiny than before but morally, perhaps that is a "right price" to pay for the responsibility of using sentient animal species in research. Whether we can look forward to Ethics Committees considering animal research, as in some other countries, remains to be seen.

D. B. Morton

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QUANTITATIVE EEG AND BRAINSTEM AUDITORY EVOKED POTENTIALS: COMPARISON OF ISOFLURANE WITH HALOTHANE USING THE CEREBRAL FUNCTION ANALYSING MONITOR†

A. R. LLOYD-THOMAS, P. V. COLE AND P. F. PRIOR

SUMMARY

We studied EEG and brainstem auditory evoked potentials (BAEP) during routine surgery at various concentrations of isoflurane (12 patients) or halothane (11 patients) or during prolonged (mean 2.5 h, range 1.9–3.5 h) administration of 1% isoflurane (five patients). Recording and analysis was performed with the cerebral function analysing monitor (CFAM). At equivalent MAC, the two agents exhibited distinctive neurophysiological profiles. Increasing concentrations of isoflurane produced a clear sequence of EEG changes (decreasing fast and increasing slow components) then burst suppression activity suggesting cortical depression. With halothane, changes in EEG amplitude were less pronounced and those in frequency content less systematic, with no periods of suppression. Simultaneous BAEP showed greater latency increase with halothane than with isoflurane. Prolonged administration of 1% isoflurane was associated with a stable EEG (no periods of suppression) and BAEP.

KEY WORDS

Anaesthetics, volatile: halothane, isoflurane. Monitoring: auditory evoked potentials, EEG.

Although the neurophysiological effects of anaesthetic agents have been documented extensively, there are few quantitative data on EEG and evoked potential changes with standard anaesthetic procedures during surgery. We have studied the effects of nitrous oxide with increasing concentrations of isoflurane and halothane during routine operations.

PATIENTS AND METHODS

Following approval by the local Ethics Committee, we studied four male and 24 female (ASA I) patients (aged 25–55 yr) during elective orthopaedic or gynaecological surgery. Premedication (90 min before operation) comprised papaveretum 0.2 mg kg^{-1} and hyoscine 4 µg kg^{-1}; standardized anaesthesia comprised thiopentone 5 mg kg^{-1}, fentanyl 5 µg kg^{-1}, tubocurarine 0.5 mg kg^{-1} (chosen to minimize tachycardia) and 66% nitrous oxide in oxygen given by intermittent positive pressure ventilation. End-tidal carbon dioxide ($F\acute{E}_{CO_2}$) was maintained at 5%.

The patients were allocated to three groups. Group I ($n = 12$) received isoflurane at end-tidal concentrations 0.5, 1.0, 1.5 and 2.0 vol%; group II ($n = 11$) received halothane at end-tidal concentrations 0.5, 1.0 and 1.5 vol%; group III ($n = 5$) received isoflurane at end-tidal concentration of 1% for a mean of 2.5 (range 1.9–3.5) h according to surgical need. Baseline measurements with nitrous oxide in oxygen were at a mean of 10.75 ± 1.25 min after induction with thiopentone; the volatile agent was introduced and 20 min stabilization with continuous EEG and end-tidal gas monitoring at each concentration preceded neurophysiological measurements. If systolic arterial pressure decreased to less

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than 100 mm Hg, anaesthesia was lightened and data from that part of the study rejected.

Monitoring

The ECG (CM$_5$), oesophageal temperature, end-tidal carbon dioxide and end-tidal concentration of volatile agent (Datex Normac) were displayed continuously; arterial pressure was measured indirectly at 2.5-min intervals and intermittent arterialized venous blood samples were taken for confirmation of $F\text{E}'_{CO_2}$.

The EEG from left and right parietal regions was processed continuously in 2-s epochs by the cerebral function analysing monitor [1] (fig. 1) (CFAM RDM Consultants); the raw EEG recorded on analog tape was replayed later onto a paper chart. The CFAM digital analysis was replayed subsequently into a mainframe computer; it comprised amplitude: maximum, 90th centile, mean, 10th centile, minimum; frequency: percent content of beta 2 (> 20 Hz), beta 1 (14.3–20 Hz), alpha 2 (10–14.3 Hz), alpha 1 (7.7–10 Hz), theta 2 (5.3–7.7 Hz), theta 1 (3.5–5.3 Hz), delta 2 (2.0–3.5 Hz), delta 1 (1–2 Hz), very low frequency (< 1 Hz) and suppressions (< 3 μV); and an indication of validity (electrode impedance, line interference and scalp muscle potentials) of each 2-s epoch.

Careful inspection of the raw EEG and the CFAM chart with digital time log, enabled selection of artefact-free epochs, agreed by two observers, from each level of anaesthesia. The mean (SD) number of 2-s epochs analysed for each concentration of isoflurane was 1207.8 (291.7), for halothane 1158.8 (302.8) and for each sample period during prolonged isoflurane 1276.5 (287.3).

After preoperative assessment of hearing, brainstem auditory evoked potentials (BAEP) were recorded between mastoid and vertex electrodes following 60-dB hearing level clicks to one ear. Because of time constraints, each BAEP was the average of only 1000 responses and some were rejected as inadequate for unambiguous measurement. Two independent observers assessed amplitude, latency and inter-peak intervals of waves I, III and V.

Statistical analysis

All EEG variables at each depth of anaesthesia were normally distributed and changes from baseline were compared by both two-way analysis of variance and paired *t* tests. Both mean values and variance were analysed for each sample.

RESULTS

(Full numerical details of results may be obtained on application to the authors.)

The patient groups did not differ significantly in respect of age, sex and weight. During anaesthesia there were no disturbances of cardiac rhythm or ischaemic changes. The maximum reduction in oesophageal temperature was 0.5 °C, the lowest value being 36 °C. There were no complications attributable to the anaesthetic or measurement techniques on postoperative examination at 1 and 24 h.

During baseline light anaesthesia with nitrous oxide, the EEG showed predominantly fast activity; there were no significant EEG differences between any of the groups and the latencies of waves I, III and V of the BAEP were 1.76 (SD 0.07), 3.87 (0.06) and 5.46 (0.14) ms, respectively. After measurements at 0.5% isoflurane and 0.5% halothane, surgery commenced without producing any significant differences in EEG values or variability; no epileptiform activity appeared in the raw EEG of any patient.

Isoflurane anaesthesia

Significant EEG changes compared with nitrous oxide were as follows: 0.5% isoflurane increased EEG amplitude (fig. 2) and reduced percentage beta 2 content (fig. 3) (both $P < 0.02$); 1% isoflurane reduced beta 1+2 ($P < 0.001$) and increased theta 1+2 ($P < 0.01$); 1.5% isoflurane further reduced beta 1 ($P < 0.01$), reduced alpha 2 ($P < 0.05$) and increased theta 1 ($P < 0.01$). Short (0.5–1.75 s) periods of EEG suppression appeared in 2% of patients (1% of the time). Isoflurane 2% further decreased beta 1, beta 2, alpha 1 and alpha 2, and minimum and 10th centile amplitudes and further increased theta 1+2 (all $P < 0.001$) and delta 2 ($P < 0.02$); suppressions of 1–147 s duration appeared in nine patients, undue hypotension (systolic arterial pressure < 100 mm Hg) having precluded administration of 2% isoflurane in the other three patients.

All EEG amplitude and frequency variables were altered significantly ($P < 0.01$, one-way analysis of variance) compared with baseline and other values as anaesthetic depth increased. Minimum and 10th centile amplitude, beta 1+2, theta 1+2, and delta 2 percentage frequency contents were most affected (highest *F* ratios). Ratios of fast to slow EEG activity (beta : delta and beta : theta) declined with increasing concentrations of isoflurane (fig. 4).

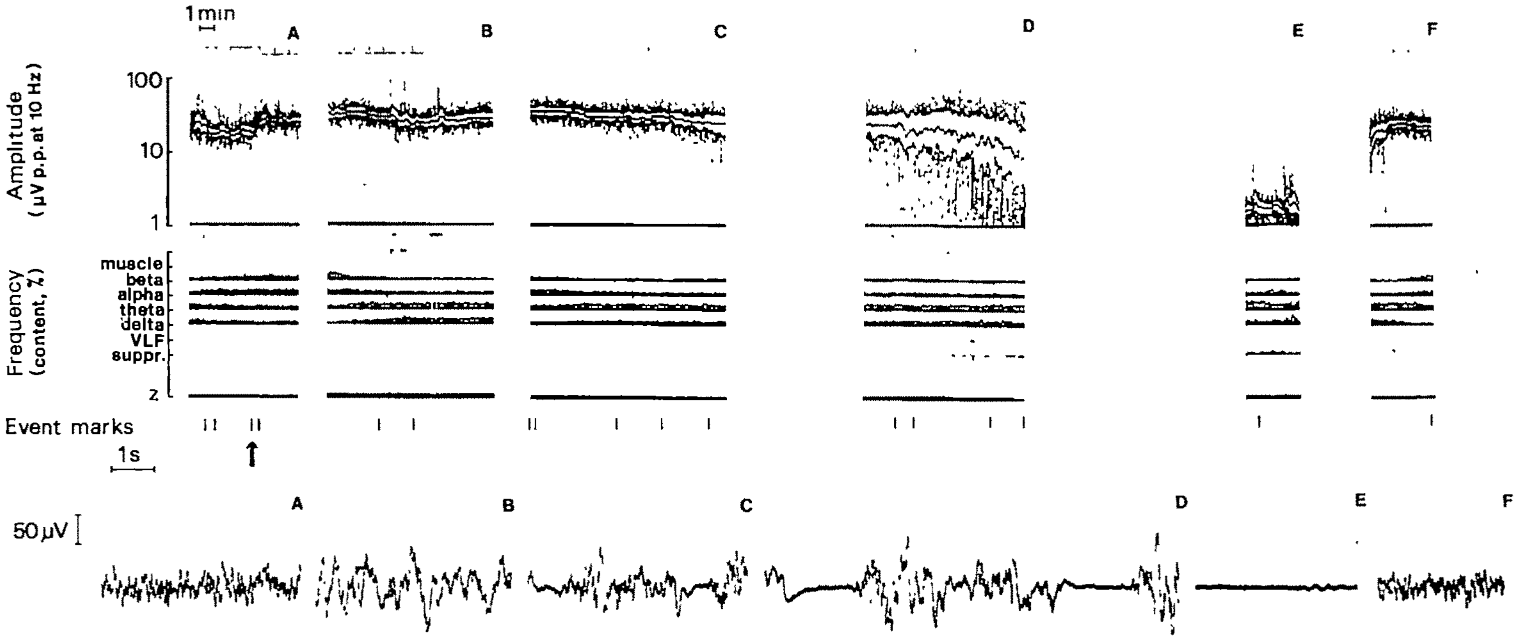

FIG. 1. Examples of CFAM recordings to show typical appearances at different concentrations of isoflurane. (Recordings not all from the same patient.) Top records: processed EEG (note that conventional frequency bands are not subdivided as for a digital output); lower records: intercurrent raw EEG samples (passband 0.8–70 Hz). A: Initially nitrous oxide in oxygen only—note the variability, particularly in amplitude, and the increase in amplitude on introduction of 0.5 % isoflurane (at arrow). B: Stable 0.5 % isoflurane—note the decrease in variability and the shift to slower frequencies. C: Isoflurane 1.0 %, increased to 1.5 %—note subtotal amplitude suppression up to 0.5 s. D: Isoflurane 1.5 %, increasing to 2 %—note effect on 10th centile and minimum amplitude and the appearance of suppressions up to 1.5 min, which are notched by ECG pickup on the EEG sample. E: Isoflurane 2.0 %—note small ripple of residual EEG and ECG. F: Recovery—note the rapid increase in amplitude precedes shift to faster frequencies. VLF = very low frequency; Suppr. = suppression.

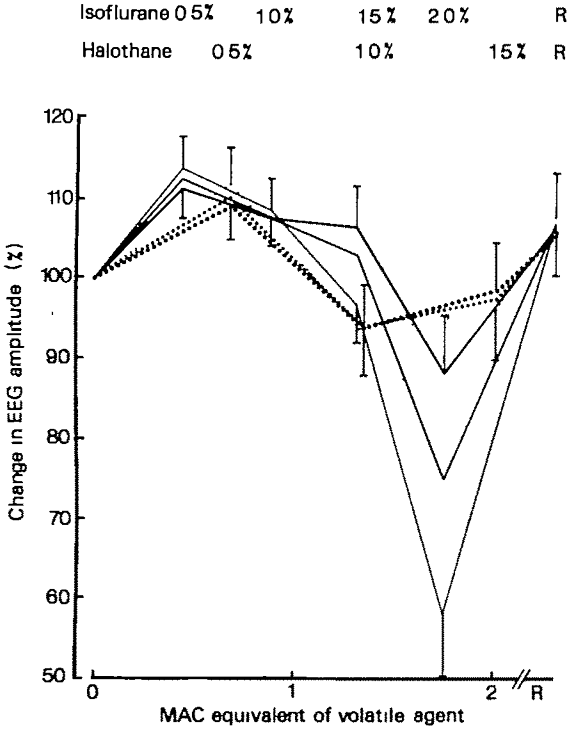

FIG. 2. Group average (1 SD) percentage change from nitrous oxide in oxygen only, in minimum (fine), mean (medium) and maximum (bold) EEG amplitude, measured by the CFAM in patients receiving isoflurane (continuous lines) or halothane (dotted lines). Concentrations of isoflurane and halothane are end-tidal (vol %). R = Recovery.

The variance of frequency content increased with increasing concentrations of isoflurane whilst that of amplitude initially decreased, then increased markedly with onset of burst suppression pattern (fig. 1). Because the unprocessed EEG and the CFAM charts suggested that variability and absolute values in the EEG changed with anaesthetic depth, changes in amplitude variability were quantified by both variance of amplitude and a ratio (amplitude variance:minimum amplitude), the former diminishing considerably (average 60%) with introduction of isoflurane and the latter decreasing in 10 patients and remaining static or increasing in the two other patients. This confirmed the visual impression of smoothing of EEG and CFAM traces by loss of moment to moment amplitude variations. With 1.5% isoflurane, high amplitude slow activity combined with short periods of suppression to increase amplitude variance and the ratio also increased in all but two patients. For group data, both amplitude variance and ratio decreased with 0.5% and 1%, but increased significantly with 1.5% and 2.0% isoflurane ($P < 0.02$ and < 0.05, respectively).

Halothane anaesthesia

Significant EEG changes were as follows: 0.5% halothane increased beta 1 activity compared with nitrous oxide alone ($P < 0.02$) (fig. 3); 1.0% halothane was associated with a decrease in amplitude compared with 0.5% ($P < 0.05$) (fig. 2); 1.5% halothane increased theta 1 and reduced beta 2 compared with nitrous oxide (both $P < 0.001$).

One-way analysis of variance confirmed that only the proportions of beta 2 and theta 1 activity altered significantly with increasing depth of anaesthesia ($P < 0.01$), none of the amplitude measures being related to halothane concentration. After an initial increase with 0.5%, both fast:slow ratios declined as the concentration of halothane increased further (fig. 4). Individual variability assessed by the variance amplitude ratio increased in three patients, was unchanged in two and decreased in five patients with 0.5% halothane. With both 1.0% and 1.5% there were no changes in individual patients in EEG amplitude or frequency variability compared with nitrous oxide alone; inter-individual variation was not reduced by halothane, but both the group mean variance and variance amplitude ratio increased.

Brainstem auditory evoked potentials

Technically satisfactory complete series of BAEP were obtained in 12 patients (six from each group). No consistent amplitude changes were observed. With isoflurane, latencies of waves I and III remained unchanged at all concentrations, but that of wave V increased significantly from 5.46 (0.14) ms to 5.87 (0.13) ms (1% isoflurane, $P < 0.02$) and 5.91 (0.09) ms (2% isoflurane, $P < 0.01$). With halothane, latency of wave III increased significantly from 3.72 (0.05) ms to 3.98 (0.82) ms (1.0% halothane, $P < 0.02$) and from 3.72 (0.05) ms to 4.1 (0.16) ms (1.5% halothane, $P < 0.01$) compared with nitrous oxide alone and wave V latency increased with increasing halothane concentrations but significantly only with 1.5% ($P < 0.01$).

Prolonged anaesthesia with 1% isoflurane

An end-tidal isoflurane concentration of 1%

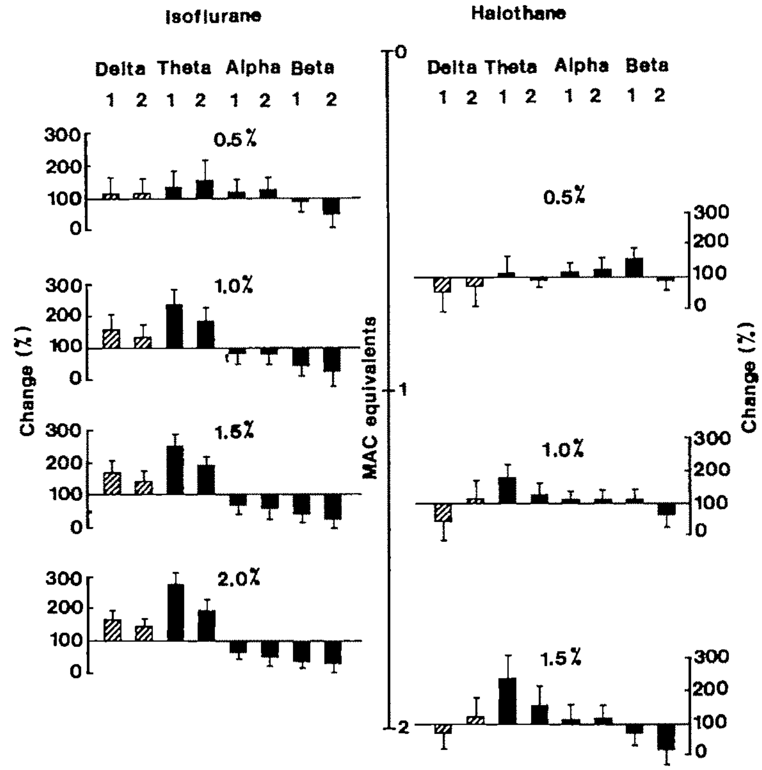

FIG. 3. Group mean (1 SD) percentage change from nitrous oxide in oxygen only, in EEG frequency content measured by the CFAM in patients receiving isoflurane or halothane.

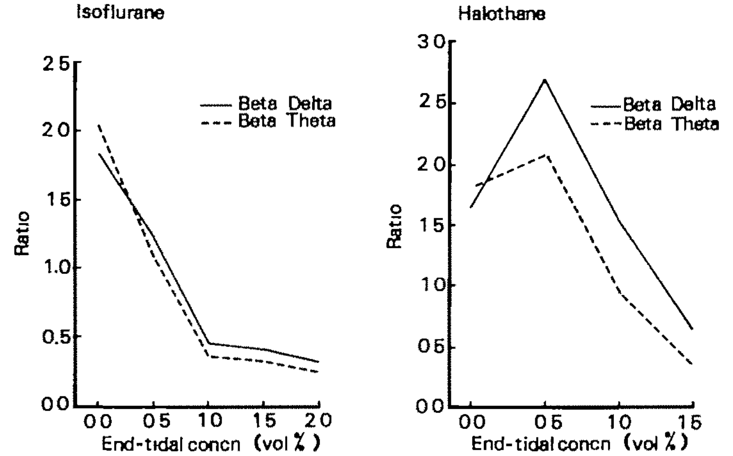

FIG. 4. Behaviour of two fast:slow EEG ratios with increasing concentrations of isoflurane or halothane. With isoflurane a relatively steady state was reached at an end-tidal concentration of 1%.

was sustained for an average of 2.5 h during routine surgery, the ratio of end-tidal to inspired isoflurane increasing from an average of 0.65 after the initial 20-min stabilization to only 0.7 during the whole period. EEG and BAEP remained stable throughout and were not significantly different from those in patients receiving 1% isoflurane for shorter periods described above.

DISCUSSION

There were striking differences between the EEG effects of isoflurane and halothane (figs 2, 3), whilst the sequence of changes with each agent appeared consistent between subjects. Our study has established a database for these two volatile agents within a balanced anaesthetic technique during routine surgical operations.

The EEG monitor (the CFAM) which we used in conjunction with conventional EEG, has the ability to quantify EEG even during the periods of burst suppression which characterize deeper levels of anaesthesia [2]. Because of its continuous display of analysed amplitude and frequency information (with visualization of the raw signal when required), it also permits detection of short-lived events and of moment to moment variability of the EEG. Methods based solely on Fast Fourier Transform or baseline crossing techniques use discrete periods (typically of the order of 4–60 s) of EEG and produce a mean analysis for each time sample, commonly displayed sequentially as a compressed spectral array. These techniques, and also related derived unitary measures such as spectral edge or median frequency, fail to reflect the full variability of the signal because of the smoothing introduced by the averaging process which may also mask short periods of suppression [3, 4].

We found a consistent and stable high proportion of alpha and beta activity during anaesthesia with nitrous oxide alone, which seemed unlikely to be a residual effect of thiopentone, at an average interval of 10 min before starting EEG measurements [5]. These fast activities and their marked amplitude variability highlight the light level of anaesthesia afforded by nitrous oxide. This is underlined by the increase in EEG amplitude on introduction of either isoflurane or halothane which was similar to that reported on induction of anaesthesia from the awake state [6]. Unlike the inconsistent EEG changes with increasing concentrations of halothane, with isoflurane anaesthesia there was a pronounced frequency shift to slow wave activity with changes in amplitude distribution (reflecting onset of burst suppression activity) reflecting increasing depth of anaesthesia.

Given the sequence of frequency changes, the ratio of fast to slow components might be considered a useful index of adequate anaesthesia and equate with the concept of an "anaesthetic pattern" propounded by Stullken and colleagues [7]. Our findings (fig. 4) suggest that there was a change in EEG state with 1% isoflurane consistent with an anaesthetic pattern beyond which little further frequency change occurred with increasing concentration, although it is recognized that EEG frequency content and amplitude may behave independently during anaesthesia [1]. In our study, frequency ratios did not change significantly at concentrations of isoflurane greater than 1%, whilst maximum amplitude depression did not occur until 2% was reached. However, these changes did not occur with halothane. With isoflurane there were inter-individual differences in the time of onset and degree of burst suppression pattern. They appeared unrelated to any physiological change, age, or undue susceptibility to central nervous system depressants, as judged by the patient's response to standardized premedication—it was thought initially that those who were most sleepy with premedication were also those who most readily demonstrated burst suppression, but further analysis did not confirm this. Indeed, our detailed EEG analysis highlighted the different neurophysiological states induced by isoflurane and halothane at equivalent MAC concentrations used in clinical practice, and casts doubt upon the relevance of the MAC nomenclature. There were consistent EEG alterations with isoflurane, suggesting a progressive depression of cerebral cortical function leading to a burst suppression pattern which was not seen with halothane. In contrast, halothane rather than isoflurane elicited more consistently progressive alterations in brainstem function as measured by BAEP.

The increases in latency in the brain stem auditory pathway were small but consistent and in keeping with those reported previously [8, 9]. The limited number of recordings may explain our inability to demonstrate consistent changes in amplitude. However, we have confirmed previous reports of an increase in the latency of wave V during anaesthesia with up to 1% isoflurane [10] and a similar prolongation in the latency of both waves III and V in patients receiving halothane [8].

We were not able to share the enthusiasm [11] for the use of BAEP. We found that processed EEG changes were of greater order and required much less skill to record during surgery. We accept that, ideally, measures of brainstem, subcortical and cortical effects of anaesthesia should be made in parallel. This might have been more practical if evoked potentials in the somatosensory rather than the auditory pathway had been used. We consider that during isoflurane anaesthesia the EEG was a more effective monitor of anaesthetic depth. During halothane, however, EEG changes were much less consistent and the small but progressive BAEP changes which occurred might be more helpful.

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ISOFLURANE PREVENTS EEG DEPRESSION DURING TRIMETAPHAN-INDUCED HYPOTENSION IN MAN[†]

A. R. LLOYD-THOMAS, P. V. COLE AND P. F. PRIOR

SUMMARY

We have studied the EEG analysed with the cerebral function analysing monitor (CFAM) during trimetaphan (TMP)-induced hypotension to a mean arterial pressure (MAP) of 40 mm Hg in 20 normocapnic patients anaesthetized with either 1% end-tidal isoflurane or 0.5% halothane. During the acute reduction in MAP, the average reduction in mean EEG amplitude with halothane was 14%, two patients showing short periods of EEG suppression; the decline in EEG amplitude correlated with declining MAP in four patients. In contrast, the average reduction in mean EEG amplitude with isoflurane was only 0.3% and there were neither periods of suppression nor any correlation between EEG amplitude and MAP. No significant changes in EEG frequency occurred in either group. Isoflurane prevented EEG amplitude depression during TMP-induced hypotension.

KEY WORDS

Anaesthetic techniques: hypotensive, trimetaphan. Anaesthetics, volatile: halothane, isoflurane Monitoring: CFAM, electroencephalography

Induced hypotension may be required to facilitate certain surgical operations, but may cause a small risk of cerebral ischaemia in some patients. The type of hypotensive agent influences the extent of the reduction in cerebral blood flow (CBF) at equivalent mean arterial pressures (MAP) [1] and this difference is reflected in associated EEG changes [2]. We had previously studied patients during induced hypotension under halothane anaesthesia and demonstrated that all patients receiving trimetaphan (TMP) showed some degree of EEG deterioration during the acute reduction in arterial pressure [3].

Unlike other volatile anaesthetic agents, isoflurane causes a dose-related reduction in cerebral metabolic requirement for oxygen (CMRo$_2$) until there is suppression of cortical electrical activity reflected in an isoelectric EEG [4]. It may have cerebral protective properties during ischaemic hypotension in the dog [5] and probably also in man during the potential regional ischaemia of carotid surgery [6, 7]. We investigated, therefore, the effect of substituting isoflurane for halothane during TMP-induced hypotension. We used light isoflurane anaesthesia with stable continuous EEG (no burst suppression) to permit neurophysiological detection of possible cerebral ischaemia and comparison with previous data obtained during TMP-induced hypotension with halothane [3].

PATIENTS AND METHODS

Following approval by the hospital Ethics Committee, we studied six female and four male patients aged 20–65 yr, during elective orthopaedic or plastic surgical operations for which we routinely use induced hypotension. The patients were healthy (ASA I or II), with no clinical or laboratory evidence of cardiovascular, cerebrovascular, renal or neurological disease. They were screened before and after operation by one investigator using a standard clinical neurological examination.

Anaesthesia and hypotension

The anaesthetic technique was similar to that used in our earlier study [3], except that 1%

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isoflurane was substituted for 0.5% halothane. This concentration of isoflurane was chosen because it produced a stable continuous EEG pattern for long periods and was not associated with clinically significant cardiovascular depression [8]. A period of 20 min stabilization preceded neurophysiological measurements.

Hypotension was induced with 0.2% trimetaphan camsylate (TMP) in 5% glucose, to a target MAP of 40 mm Hg. Practolol was given in 5-mg increments if MAP failed to reach 40 mm Hg or if the heart rate exceeded 80 beat min^{-1}. When clinically indicated, TMP was stopped and the arterial pressure allowed to increase.

Monitoring, measurements and analysis

ECG, oesophageal temperature, end-tidal concentrations of carbon dioxide and of volatile agent (Datex Normac) and intra-arterial pressure were monitored continuously. Systolic and diastolic arterial pressures were measured subsequently at 10-s intervals, by two independent observers, from the chart recording. MAP was calculated from the formula MAP = diastolic + (systolic/3). MAP was also remeasured directly from the original chart recordings of patients receiving halothane in our previous study [3].

The cerebral function analysing monitor (CFAM RDM Consultants) recorded raw and analysed EEG from left and right parietal electrodes and also provided a digital output of 15 EEG amplitude and frequency measures [9]. Amplitude is given in units, derived from the formula $\mu V = 10((\text{CFAM unit} - 10)/50)$, which convert the inherent asymmetric (Rayleigh) distribution of the amplitude fluctuations of the EEG to a normal (Gaussian) distribution. Frequency in any band is given as a percentage of the total frequency content. The raw EEG, recorded simultaneously on analog tape, was replayed on to a paper chart. Careful inspection of this, the CFAM chart and its digital time log enabled selection of artefact-free periods, agreed by two observers, for computer analysis. Two-second epochs were amalgamated into 10-s (during the acute reduction in arterial pressure, when the physical state was changing rapidly) and 1-min epochs (following the acute reduction and for the duration of hypotension), so deriving a mean and variance of each EEG measure for each period analysed. The timing of the median epoch in each 10-s group corresponded with an arterial pressure measurement. Tape-recorded raw EEG from our previous study [3] was replayed through the CFAM and analysed, timing of EEG samples and correlation with the remeasured MAP values being made by reference to the original chart recordings.

The statistical distribution of each variable was assessed before applying appropriate parametric or non-parametric tests. Changes in the 15 EEG parameters at end-tidal 1% isoflurane after 20 min of stabilization were compared with the data obtained during the preceding 3 min of stable anaesthesia at normotension by analysis of variance, paired *t* tests and correlation with simultaneous MAP values. Statistical comparisons between isoflurane and the historical halothane group data were not undertaken.

RESULTS

There was no significant difference in age, preoperative MAP, steady state MAP before induction of hypotension, or rate of reduction in MAP with TMP in the patients receiving isoflurane in the present study (isoflurane patients) and those receiving 0.5% halothane in our previous study [3] (halothane patients).

Six of the halothane patients and all of the isoflurane patients required β-block. The target MAP was reached in 5.4 (SD 4.5) min after starting TMP in the isoflurane patients, but at 9.1 (7.9) min in the halothane patients. Two isoflurane patients and six halothane patients did not reach 40 mm Hg MAP and two (isoflurane) momentarily overshot this value; MAP returned to 40 mm Hg within 5 min after stopping TMP and infusing colloid. Hypotension was maintained for an average of 83 (34.4) min in the isoflurane patients and for 70 (14) min in the halothane patients. There were no disturbances of cardiac rhythm and no ischaemic changes in the ECG of any patient. The maximum reduction in oesophageal temperature was 0.6 °C; the lowest temperature recorded was 36.1 °C.

Electroencephalogram

In the steady state, before induction of hypotension, there were significant differences in all the EEG amplitude measures between isoflurane and halothane patients, comparable to those seen in our preliminary anaesthetic study [8], except for a slightly lower amplitude with halothane.

In isoflurane patients, during the acute reduction in arterial pressure, the group average mean EEG amplitude decreased by 0.32 (0.05)%. Of the 10 patients, six had a reduction in mean amplitude of 0.3–3.8% and four had an increase of 0.71–2.92%. Thus, during the period in which the group MAP decreased by 28–52%, the greatest reduction in mean EEG amplitude in any individual isoflurane patient was 3.2% (from 82.3 to 79.7 CFAM units). Analysis of variance showed that there were no significant changes in any of the group average amplitude or frequency measures and at no time was burst suppression pattern observed.

In the halothane patients, during the acute reduction in arterial pressure, the group average mean EEG amplitude decreased by 14%. There were significant changes in all group average amplitude measures, but none in frequency. Each of the 10 halothane patients exhibited a reduction in mean amplitude of 4.2–36%. During the period in which the group MAP decreased by 20–54%, the greatest reduction in mean EEG amplitude in an individual patient was 36% (from 45.4 to 29.0 CFAM units) and the smallest was 4.2% (from 57.5 to 55.1 CFAM units). In the two patients with the greatest decline in mean EEG amplitude, short periods of suppression (0.29–1.78% of time) were seen as MAP reached lowest values.

There was no significant correlation between acutely declining MAP and any EEG amplitude or frequency measure in the isoflurane patients, but a significant correlation in four halothane patients. In the former, the group mean amplitude did not change with the decline in MAP, whereas in the latter it decreased when MAP reached 60 mm Hg (fig. 1). Data from the two isoflurane patients who briefly overshot the target show that at MAP less than 40 mm Hg there was a decline in the amplitude of the EEG comparable to that seen at 60 mm Hg with halothane.

In the 5 min following the acute hypotension, group mean EEG amplitude and frequency data in isoflurane patients showed no significant difference from the control data obtained before induction of hypotension. Comparable data were not available for analysis from the halothane patients. By the end of the period of hypotension (mean of 95.4 (27.6) min) all isoflurane patients showed a slight decline in mean amplitude of the EEG (group mean decrease 0.7 (0.66) µV—a 3.54% decrease from baseline values). This could not be correlated with age, lowest MAP, percentage acute reduction in MAP, dose of TMP, duration of hypotension or rate of decrease in MAP, although the two patients with the largest overall decrease in mean amplitude (6.3% and 4.7%) had the greatest rates of decrease in MAP.

At the end of surgery, isoflurane patients awoke rapidly (mean time of anaesthesia 126.7

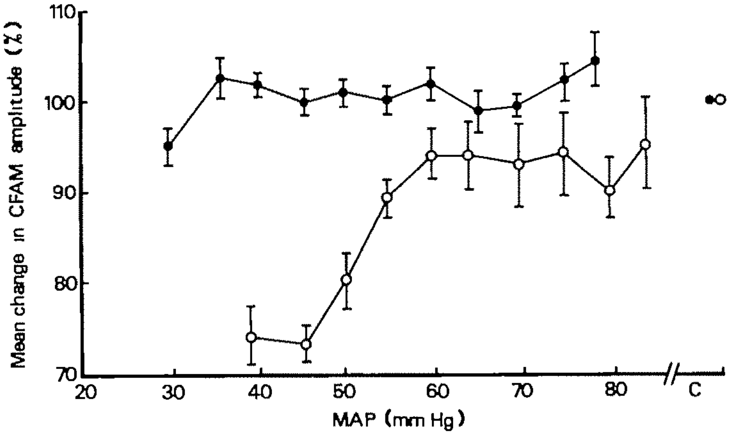

FIG. 1. Group mean percentage change (1 SEM) in mean amplitude of CFAM trace at median points of 5-mm Hg MAP steps during TMP-induced hypotension in 10 patients (227 measurement points) receiving isoflurane (●) and 10 patients (189 measurement points) receiving halothane (○) [3]. C = Control.

(54.6) min, mean time to recovery 10.7 (5.6) min). There was no neurological deficit in any patient after isoflurane or halothane anaesthesia.

DISCUSSION

Cerebral blood flow may diminish when induced hypotension reaches an individual threshold of arterial pressure; this reduction can be correlated with the mean amplitude of the EEG measured by the cerebral function monitor [2]. Cerebral ischaemia occurs if CBF decreases to less than a critical value and the earliest signs are short periods of electrical silence on the EEG. One advantage of isoflurane at a stable concentration of 1% and normotension is that it is not *per se* associated with periods of EEG suppression [8], thus allowing neurophysiological monitoring when there is a potential risk of ischaemia.

Previous experimental and clinical studies of TMP-induced hypotension during administration of halothane have shown that there may be a reduction in cerebral perfusion and deterioration in the EEG [2, 3]. Re-analysis of the tape-recorded EEG data from our earlier investigation [3] using the CFAM has confirmed that all patients showed some degree of deterioration during the acute reduction in MAP, and in the two patients with the most severe amplitude decline, short periods of suppression of all EEG activity appeared *de novo*. Periods of suppression are not typical of uncomplicated halothane anaesthesia [8]. In contrast, the present investigation has shown that with 1% isoflurane there was no deterioration in the EEG and, specifically, no period of EEG suppression during a similar acute reduction in arterial pressure.

We are aware of the difficulties inherent in comparisons with historical data. However, our previous assessment of the data from halothane patients [3] had suggested that there was a theoretical risk to patients from a combination of halothane and TMP in the presence of hypotension, and it was considered ethically unacceptable to repeat the study. In the present study, there was only a minimal, non-significant, decline in EEG amplitude in only six of 10 isoflurane patients, in contrast with the major decline in all halothane patients. This suggests that the balance of cerebral oxygen supply and demand is maintained during TMP-induced hypotension when the background anaesthetic is isoflurane. These findings are supported by recent reports, in patients during carotid artery surgery, that EEG deterioration occurred at a lower regional CBF with light isoflurane anaesthesia compared with halothane or enflurane [6, 7]. Although we did not measure cardiac output, it probably decreased after administration of TMP and β-blocking drugs [10]. The difference in cardiac output between patients at 0.66 MAC halothane and those at 0.87 MAC isoflurane is unlikely to be large [11]. Moreover, neither isoflurane (up to 1.1 MAC) nor halothane (up to 0.6 MAC) increases CBF in normocapnic, normotensive patients [11]. Therefore, the findings in patients anaesthetized with isoflurane are unlikely to have been caused by selective increase in CBF or preservation of cardiac output.

Cerebral autoregulation maintains CBF over a wide range of MAP. In all the halothane patients, EEG changes commenced at a mean threshold of 60 (5.7) mm Hg [3], which is close to the pressure at which autoregulation normally fails in normotensive man. At normocapnia, 1 MAC of halothane abolishes cerebral autoregulation, although it is restored partially by reduction to less than 0.5 MAC [12]. Experimental studies have shown that isoflurane produces significantly less impairment of cerebral autoregulation than MAC equivalents of halothane [13]. The threshold below which CBF becomes pressure dependent is influenced by several factors: rate of and method used to induce hypotension [14]; previous arterial pressure [15]; age of the patient and rate of decrease in MAP. Whilst preservation of autoregulation by isoflurane might account for the maintenance of the EEG at MAP 50–60 mm Hg, it would be surprising if CBF had not become pressure dependent in the range 40–50 mm Hg. Experimental studies have suggested that nitrous oxide exaggerates the increase in CBF during both isoflurane and halothane anaesthesia [16], but nitrous oxide was administered at equal MAC in both groups of patients and thus should not have biased the outcome.

Cerebral protection from global ischaemia has been claimed using isoflurane in an experimental model [5] and using thiopentone during cardiac surgery in man [17]. In both investigations, however, the presumed protective agents were given in doses sufficient to suppress partially the spontaneous EEG, at which point the pharmacological reduction in $CMRo_2$ is maximal. However, the dose–response curve of reduction in

$CMRo_2$ with increasing concentrations of volatile agent is not linear [18]. In dogs, the greatest rate of decline in $CMRo_2$ occurs when the EEG changes from an awake to an "anaesthetic" pattern, which occurred at 0.72 MAC for halothane and at 0.47 MAC for isoflurane [18]. End-tidal 1% isoflurane (0.74 MAC) was associated with a 30% decline in $CMRo_2$, whereas with end-tidal 0.61% halothane (0.7 MAC), the reduction was only 5–10% [18]. Up to 75% of the possible $CMRo_2$ reduction from isoflurane is achieved by administering less than 1 MAC.

Light isoflurane anaesthesia (insufficient to produce burst suppression activity and comparable to that in the present study) during carotid artery surgery has been reported as being associated with fewer ischaemic events in the EEG and considered to offer a degree of cerebral protection from transient incomplete regional cerebral ischaemia [6, 7]. Isoflurane, in both feline and rodent models, has been shown to be a more potent metabolic depressant than halothane at equal MAC concentrations [13, 19] and, in the rat, is associated with a relatively greater depression of neocortical CBF [20]. In our preliminary anaesthetic study [8], the EEG conformed to an anaesthetic pattern (decrease in faster and increase in slower activities) at much lower MAC equivalent concentrations of isoflurane than of halothane. In both animal and human studies of isoflurane-induced hypotension [21–23], CBF appeared to be maintained despite a reduction in MAP (except in one study when it decreased). Furthermore, using isoflurane to induce prolonged hypotension to either 40 or 50 mm Hg MAP did not result in any deterioration of cerebral energy stores in an animal model [21]. If these experimental studies are applicable to man, a more profound reduction in $CMRo_2$ by light isoflurane anaesthesia (compared with other volatile agents) may be responsible for the maintenance of adequate cerebral oxygenation.

We have shown that light isoflurane anaesthesia prevented EEG depression which occurred in all patients with halothane anaesthesia during TMP-induced hypotension. Light anaesthesia avoids profound circulatory depression and allows the use of more rapidly controllable hypotensive drugs. Furthermore, preservation of the spontaneous EEG, in particular avoidance of periods of EEG suppression, allows continuous neurophysiological monitoring.

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LOWER OESOPHAGEAL CONTRACTILITY AND DETECTION OF AWARENESS DURING ANAESTHESIA†

P. A. ISAAC AND M. ROSEN

SUMMARY

We have investigated the value of lower oesophageal contractility (LOC) in detecting awareness during anaesthesia in 20 human volunteer patients. LOC was measured either with subjects awake or after induction with propofol, during induction with propofol, and then as consciousness returned. Statistically significant changes were observed in the frequency of spontaneous contractions, peak and mean amplitude of spontaneous and provoked contractions, and the oesophageal contractility index as subjects lost consciousness and also as it was regained. The differences in LOC which occurred when subjects were conscious and unconscious support the view that LOC is related to the depth of anaesthesia, but its unreliability at the interface between consciousness and unconsciousness prevents selective detection of awareness, although the response in the presence of painful stimuli has not been tested.

KEY WORDS

Anaesthesia: depth. Gastrointestinal tract · oesophageal contractility.

Awareness during anaesthesia has been defined by Wilson [1] as "The ability of patients to recall, with or without prompting, any event occurring during anaesthesia." However, it is possible for a patient to be aware of his or her surgery during an anaesthetic but not recall the awareness after operation if the anaesthesia is subsequently deepened [2]. Previous studies have reported a wide range of incidences of awareness depending upon the method of detection [3], up to 40% using postoperative hypnosis [4]. More recently, using the isolated forearm technique for detection [5], Russell described a 44% incidence of "wakefulness" in patients anaesthetized with nitrous oxide and fentanyl. This is similar to the 46% incidence reported by Shultetus and colleagues [6], using the same detection method but a different anaesthetic technique.

Many methods of assessing depth of anaesthesia have been investigated, including the cerebral function analysing monitor [7], power spectrum analysis [8], frontal EEG and frontal EMG [9], the electroretinogram [10] and changes in skin electrical conductance [11]. Recently, auditory evoked potentials have been reported to be accurate in the detection of inadequate anaesthesia allowing awareness, in a study using methodology similar to that described below [12]. The measurement of lower oesophageal contractility (LOC) has been suggested as a means of detecting episodes of too light and too deep anaesthesia [13] and has been used to provide feedback control of an i.v. anaesthetic infusion system [14]. As the occurrence of awareness during anaesthesia, with or without recall, can be considered to be a potential consequence of inadequate anaesthesia, we have investigated the value of LOC in detecting actual awareness by examining LOC in human volunteers as they lost consciousness under the influence of propofol, and regained consciousness.

PATIENTS AND METHODS

Patients about to undergo intermediate or major surgery gave informed consent for the study, which was approved by the District Ethics

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Committee. Patients were informed that they would awaken transiently from anaesthesia shortly after induction, but before surgery had commenced, and would then have anaesthesia induced once again. Patients with a history of oesophago-gastric disease and those taking medication with anticholinergic actions were excluded. LOC was measured by passing an oesophageal probe with a distal water-filled sensing balloon and a proximal provoking balloon into the lower oesophagus as described elsewhere [13]. This system was connected via a pressure transducer to a Lectron 301 oesophageal monitor (Antec Systems Ltd, Oxford).

Patients sucked an amethocaine lozenge (60 mg) and had the pharynx sprayed with 10 % lignocaine from a metered dose spray; subsequently they attempted to swallow the probe whilst awake. A small bolus (up to 10 mg) of i.v. diazepam was given to any patient who had difficulty in swallowing the probe. A pilot study had shown that pharyngeal local anaesthesia or a small dose of diazepam did not significantly affect LOC [personal observations]. If the patient was still unable to swallow the probe, an induction dose of propofol 2.5 mg kg^{-1} was administered and the probe was introduced. When the patient was settled with the probe in place and was awake (had not received propofol to facilitate insertion of the probe), an infusion of propofol, set initially at an average rate of 15 mg kg^{-1} h^{-1} and adjusted to produce induction of anaesthesia over approximately 5 min, was started while the patient breathed oxygen via a Mapleson A circuit. If propofol had been used to introduce the probe, the patient was allowed to awaken with the probe in place. After an interval of approximately 2–3 min, anaesthesia was re-induced with an infusion of propofol.

At 30-s intervals, each subject's conscious level was assessed during induction of, and emergence from, anaesthesia by observing the subject's response to a command to squeeze the investigator's hand. The time at which hand squeezing appeared or disappeared was noted. This was defined as the "cross-over point."

When light anaesthesia had been induced, as judged by loss of the hand squeezing response, the infusion was discontinued and the patient was allowed to regain consciousness. The point at which this was judged to have occurred was when the hand squeezing response returned. All analyses of recordings were made in the 2-min periods before and after the cross-over point, and compared using the Wilcoxon rank sum test. The study ended at this point and anaesthesia was re-induced for surgery. All subjects were visited on the day following surgery and enquiry made for recall of induction of anaesthesia and occurrence of dreaming during anaesthesia.

RESULTS

Twenty subjects were studied (mean (SD) age 49.4 (13.8) yr, weight 69.0 (16.2) kg and height 167.1 (9.6) cm). Fourteen patients received diazepam

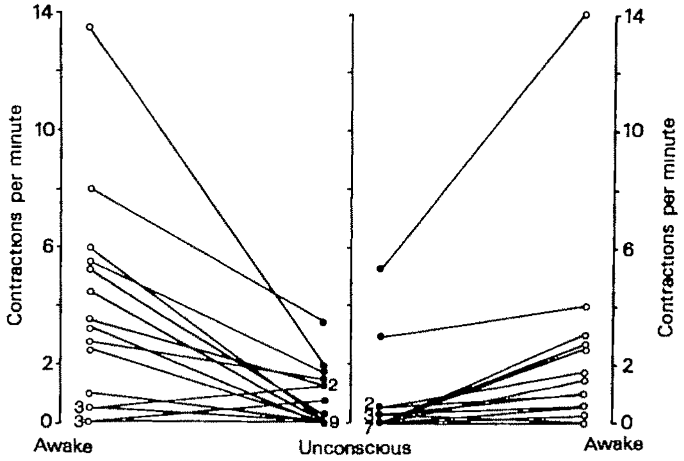

FIG. 1. Change in frequency of spontaneous contractions as patients lost consciousness (left) and regained consciousness (right). Each line represents an individual subject, except where more than one subject is indicated by number.

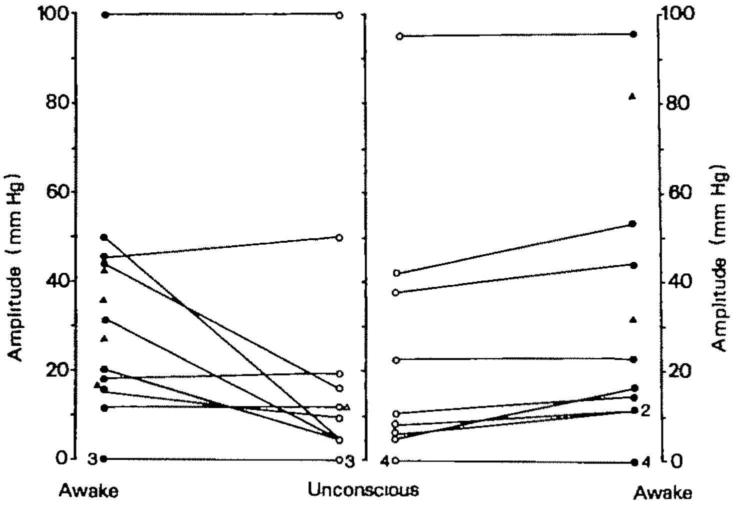

FIG. 2. Change in peak amplitude of provoked contractions as patients lost consciousness (left) and regained consciousness (right). Each line represents an individual subject, except where more than one subject is indicated by number. ▲ = Subjects in whom contractions were present in the awake phase only; △ = subject in whom contractions were present in the unconscious phase only.

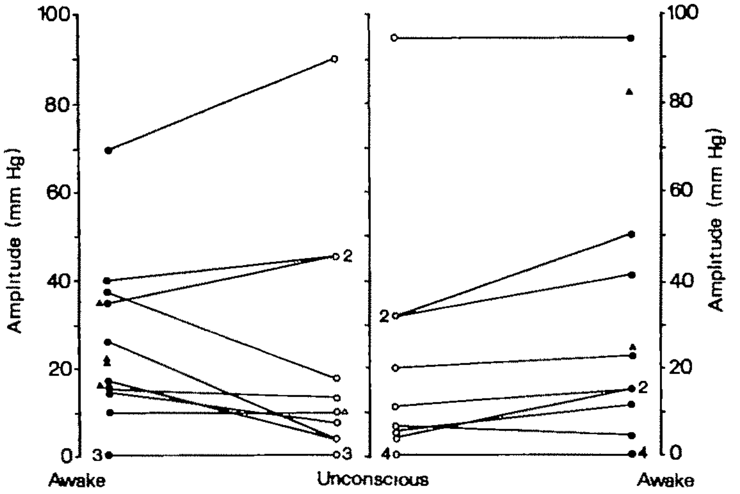

FIG. 3. Change in mean amplitude of provoked contractions as patients lost consciousness (left) and regained consciousness (right). Each line represents an individual subject, except where more than one subject is indicated by number. ▲ = Subjects in whom contractions were present in the awake phase only; △ = subject in whom contractions were present in the unconscious phase only.

and eight patients received a bolus of propofol to enable insertion of the probe. LOC recordings were made in 17 subjects as consciousness was lost, and in 14 subjects as it was regained. In three patients, recordings were not made as consciousness was lost because of a probe leak in one patient and inadequate time before surgery in the other two. In six patients, recordings were not made as consciousness was regained because of probes leaking in two patients, coughing in two patients and shortage of time in two.

Measurements made from the LOC recordings included frequency, mean and peak amplitude of all spontaneous lower oesophageal contractions (SLOC) and the mean and peak amplitude of all provoked lower oesophageal contractions (PLOC) in each 2-min period. In addition, oesophageal contractility index (OCI) [15] was calculated. Figures 1–4 show the spontaneous frequency, provoked amplitude and OCI for each patient before and after the cross-over period—that is, as patients lost consciousness and regained it. The

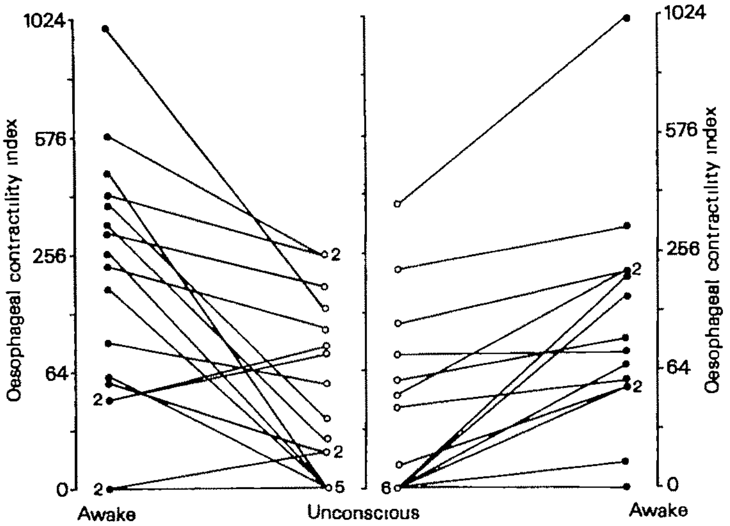

FIG. 4. Change in oesophageal contractility index as patients lost consciousness (left) and regained consciousness (right). Each line represents an individual subject, except where more than one subject is indicated by number.

TABLE I. *Mean* (SD) *changes in contraction frequency* (*contractions per minute*), *amplitude* (*mm Hg*) *and oesophageal contractility index* (*OCI*) *as subjects lost consciousness.* n = *17. SLOC = spontaneous lower oesophageal contractions; PLOC = provoked lower oesophageal contractions*

Variable	Conscious	Unconscious	*P*
SLOC frequency	3.4 (3.6)	0.7 (1.0)	0.001
SLOC peak amplitude	47 (33)	21 (34)	0.007
SLOC mean amplitude	25 (17)	11 (18)	0.005
PLOC peak amplitude	27 (25)	14 (25)	0.006
PLOC mean amplitude	21 (18)	15 (24)	0.042
OCI	257 (254)	73 (88)	0.001

TABLE II. *Mean* (SD) *changes in contraction frequency* (*contractions per minute*), *amplitude* (*mm Hg*) *and oesophageal contractility index* (*OCI*) *as subjects regained consciousness.* n = *14. SLOC = spontaneous lower oesophageal contractions; PLOC = provoked lower oesophageal contractions*

Variable	Unconscious	Conscious	*P*
SLOC frequency	0.7 (1.5)	2.3 (3.6)	0.001
SLOC peak amplitude	15.7 (24)	36 (30)	0.009
SLOC mean amplitude	15 (26)	25 (26)	0.043
PLOC peak amplitude	16 (27)	27 (31)	0.006
PLOC mean amplitude	15 (26)	26 (31)	0.005
OCI	66 (110)	180 (252)	0.001

changes in mean contraction height and frequency and the mean OCI of the subjects in the conscious and unconscious states as the subjects regained consciousness are compared in table I, and changes as the subjects lost consciousness in table II.

Before and after the cross-over period, there were statistically significant changes in the mean values of all variables. However, for some subjects the changes were in a direction opposite to those in other patients, or of such small magnitude as to be clinically insignificant. For example, figure 1 shows a slight increase in frequency of contraction in two subjects as they became unconscious, and in both directions of change of consciousness there were subjects in whom no difference in frequency was detected. However, the general trend observed was for contractions to decrease in frequency as consciousness was lost and increase as consciousness was regained. No particular frequency corresponded to any particular conscious level. The variations between individual subjects were more apparent when changes in provoked contractions were examined (fig. 2, 3).

At the postoperative visits no patient had recall of induction of anaesthesia or experienced dreams during anaesthesia and surgery.

DISCUSSION

The design of this study allowed the conscious state of the patient to be altered with the use of anaesthetic drugs and an end-point to be identified, but it does have several disadvantages.

First, the point at which the conscious patient becomes unconscious cannot be determined, because these terms are not precise and the i.v. induction of anaesthesia involves continuous and gradual changes. The response to a command (hand squeezing) was used as a readily detectable and normally accepted sign of return of consciousness, and the lack of a response as a sign of loss of consciousness. We accept that the change in conscious level may have occurred shortly before the response was lost or appeared and did not represent the exact point at which consciousness was lost or regained, but an attempt to elicit the response was made at frequent intervals in all subjects. Therefore the cross-over point represents the same stage in each patient. In the presence of a surgical stimulus, the change in response to command might have occurred at a different stage. However, it was not possible to study this because it would have been unethical intentionally to allow patients to awaken in the presence of a painful stimulus solely for the purposes of this study.

Second, the level of anaesthesia induced was necessarily light to allow rapid return of consciousness. Therefore, the changes in LOC may not have been as large as if the patient had awakened from a deeper plane of anaesthesia.

Third, patients were not awakening either to the presence of a painful surgical stimulus or to the realization that they were awake and paralysed. Notwithstanding these inherent problems in our methodology, we believe this is a useful model for the study of the physiological changes accompanying awareness under anaesthesia.

Evans, Davies and Wise [13], in common with other workers [16–18] have described a relationship between depth of anaesthesia and frequency of spontaneous contractions and amplitude of provoked contractions, but not amplitude of spontaneous contractions. However, we have demonstrated a statistically significant increase in amplitude of spontaneous contractions in the awake compared with the unconscious phase. At these light stages of anaesthesia in the unstimulated patient, it appears that the "all or none" response of SLOC contractions described by Evans, Davies and Wise [19] is not operative, and a graded response may be seen, although it is not clear from our results if this is a clinically significant finding or a consequence of artificial stimulus-free study conditions.

In some patients the changes in frequency and amplitude of contractions observed in the awake and unconscious phases were minor; occasionally there was a decrease in frequency or amplitude when an increase would have been expected, and *vice versa*. So, although the changes were statistically different when the data for all patients were pooled, overall the changes were not clinically significant for the group.

Previous studies have drawn attention to the limitations of LOC in determining depth of anaesthesia in an individual patient. Aitkenhead, Lin and Thomas [16] showed that, while there appeared to be a gradual increase in SLOC which preceded the clinical signs, SLOC still occurred in some patients during apparently inadequate anaesthesia. Similarly, the likelihood of increased PLOC amplitude increased as anaesthesia lightened, but PLOC amplitude would not have been accurate in predicting inadequate anaesthesia in most patients. Schwieger and colleagues [20] demonstrated that, during fentanyl anaesthesia, SLOC rate was of limited value in determining adequacy of anaesthesia in nearly 50% of the patients studied. Thomas and Aitkenhead [18] observed that the intensity of surgical stimulation may be important in determining the level of oesophageal activity.

The patients' lack of recall of induction of anaesthesia and absence of dreaming may have been a result of the administration of diazepam to some patients. Also, after the study period all patients underwent intermediate to major surgery, and this may be a more important factor.

We conclude that, although there was an overall trend towards an increase in frequency and amplitude of contractions with an increase in conscious level at the "very light" end of the anaesthetic spectrum, the relationship was not sufficiently reliable for the detection of consciousness. With our model, LOC could not be demonstrated to be useful in determining when consciousness had returned to anaesthetized patients.

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ISOFLURANE WITH EITHER 100% OXYGEN OR 50% NITROUS OXIDE IN OXYGEN FOR CAESAREAN SECTION

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SUMMARY

Two hundred mothers undergoing general anaesthesia for Caesarean section were allocated randomly to receive either 100% oxygen (group 100) or 50% nitrous oxide in oxygen (group 50), both supplemented with isoflurane. In each group the concentrations of isoflurane were chosen to deliver 1.5 MAC for the first 5 min after induction and 1.0 MAC thereafter. The mean umbilical venous $P\mathrm{O}_2$ was greater in group 100 for emergency sections ($P = 0.001$). Babies born to mothers in group 100 required less resuscitation than those in group 50 ($P = 0.04$) and there was a tendency to higher Apgar scores at 1 min in group 100, although this was not statistically significant. There were no instances of awareness, although two patients in group 100 and three in group 50 reported dreaming. This study confirms earlier findings that the use of 100% oxygen can significantly improve fetal oxygenation during Caesarean section, with particular benefit in emergency cases. This is associated with a lower incidence of neonatal resuscitation.

KEY WORDS

Anaesthesia, obstetric: Caesarean section. Anaesthetic techniques: maternal oxygenation. Anaesthetics, volatile: isoflurane.

General anaesthesia for Caesarean section usually includes 50% oxygen and nitrous oxide, supplemented by a low concentration of a volatile agent. This is based upon data demonstrating that an increase in maternal $F\mathrm{I}_{\mathrm{O}_2}$ to more than 0.6 did not improve fetal oxygenation [1–3]. However, in those studies the concentration of volatile agent was not increased to compensate for the loss of the anaesthetic effect of nitrous oxide and so patients must have been anaesthetized more lightly—perhaps aware—resulting in an increase in plasma catecholamine concentrations with placental vasoconstriction. Furthermore, measures were not taken to avoid aortocaval occlusion, which could further impair placental circulation.

A pilot study in 40 patients showed that a higher umbilical venous oxygen tension was achieved with a maternal $F\mathrm{I}_{\mathrm{O}_2}$ of near 1.0 without increased bleeding or awareness [4].

This study has compared current practice with an $F\mathrm{I}_{\mathrm{O}_2}$ of 1.0 in all patients undergoing Caesarean section under general anaesthesia. Isoflurane was chosen as the volatile supplement because of its low blood solubility which would result in rapid equilibration between inspired and alveolar concentration.

PATIENTS AND METHODS

Approval was obtained from the Divisions of Anaesthetics and Obstetrics and Gynaecology and the Area Ethics Committee. Each patient received an explanation before entering the trial. The anaesthetic was administered by the duty obstetric anaesthetist or research fellow (S.E.P.).

Two hundred mothers undergoing elective or emergency Caesarean section under general anaesthesia were allocated randomly to receive isoflurane in either 100% oxygen ($n = 103$) or 50% nitrous oxide in oxygen ($n = 97$). The two

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regimens were allocated to alternate groups on alternate weeks.

Isoflurane 1.8% in 100% oxygen was reduced to 1.2% after 5 min (group 100), or 1.2% isoflurane in 50% nitrous oxide in oxygen was reduced to 0.6% after 5 min (group 50). These concentrations had been calculated to deliver 1.5 MAC for the first 5 min after induction and 1.0 MAC thereafter. The purpose of using a greater concentration initially was to compensate for the loss of nitrous oxide and the second gas effect.

Anaesthetic technique

Each patient received magnesium trisilicate 30 ml before transfer to theatre. The mother was positioned on the operating table with lateral tilt and the lungs preoxygenated for 3 min. ECG leads and the cuff of a Hewlett–Packard automatic arterial pressure recorder were attached and the preoperative mean arterial pressure measured. A standard aneroid sphygmomanometer cuff was placed on the forearm, distal to the automatic cuff, and inflated to 200 mm Hg immediately before induction, to isolate that hand from neuromuscular blocking drugs [5]. In keeping with our customary practice, no taped message was played to the anaesthetized patients, and they were not asked beforehand to move the hand if they felt pain, as it was considered that this would add to existing stress. Cricoid pressure was applied and anaesthesia was induced with thiopentone 3–4 mg kg^{-1} followed by suxamethonium 1.5 mg kg^{-1}. Following tracheal intubation, pancuronium 4–6 mg was administered. End-tidal carbon dioxide was measured and maintained at 4.0 kPa. The concentration of isoflurane was monitored with a Normac anaesthetic agent monitor (Datex) and any movement of the isolated hand was treated by increasing the concentration of isoflurane by 50% for 5 min.

After delivery of the infant, either syntocinon 10 u or ergometrine 500 µg was given according to the choice of the obstetrician. After delivery the anaesthetist was unrestricted in technique.

At delivery, umbilical venous and arterial blood samples were taken. Each baby was assessed clinically by a paediatrician unaware of the anaesthetic technique. Each mother was visited after operation by a research midwife and questioned regarding recall. Haemoglobin concentration and packed cell volume were measured at 24 and 48 h as an estimate of operative blood loss.

TABLE I. *Mean* (SD) *haemoglobin concentration and packed cell volume* (*PCV*) (*transfused patients excluded*)

	Group 50	Group 100
Decrease in haemoglobin at 48 h	1.19 (2.35)	1.10 (1.30)
Decrease in PCV at 48 h	3.18 (5.57)	2.91 (3 78)

Statistics

Continuously variable data were analysed using unpaired Student's *t* test and non-continuous data using chi-square test.

RESULTS

Maternal data

The reductions in haemoglobin and packed cell volume at 48 h were calculated as estimates of blood loss; there was no significant difference between groups (table I).

Eleven patients in group 50 and 30 patients in group 100 showed movement of the isolated forearm, which was treated by a 50% increase in the concentration of isoflurane. At 24-h follow-up, four patients (two in each group) recalled dreaming on direct questioning (two had moved the isolated arm and two had not). One patient (group 50) reported a sensation of painful pressure, but believed she had been dreaming. She had not moved her arm.

Neonatal data

Data relating to 201 babies were collected; there was no significant difference in the mean gestational age between groups or in the induction–delivery and incision–delivery intervals (table II).

Significantly more Caesarean sections were performed for fetal distress in the 50% oxygen group than in the 100% oxygen group (chi-squared = 6.0, $0.05 > P > 0.01$) (table III).

Umbilical arterial blood-gas data did not differ significantly between groups (table IV). The mean umbilical venous Po_2 was greater in group 100 for elective (5.84 *vs* 4.89 kPa) and for emergency sections (5.01 *vs* 4.0 kPa), the difference being statistically significant in the latter category ($P = 0.001$). The arteriovenous oxygen tension

TABLE II. *Neonatal data (mean values* (SD))

	Elective surgery		Emergency surgery	
	Group 50	Group 100	Group 50	Group 100
Gestation (weeks)	38.5 (2.27)	39 2 (1.40)	38.5 (2.91)	38.4 (2.76)
Induction–delivery (min)	11.76 (3 08)	12 49 (3.97)	10.02 (5.02)	10 10 (3 41)
Incision–delivery (min)	2.59 (2.87)	2.21 (2.87)	1 90 (1.05)	1.82 (1.05)

TABLE III. *Indications for Caesarean section*

	Elective surgery		Emergency surgery	
Indication	Group 50	Group 100	Group 50	Group 100
Failure to progress	0	0	22	22
Cephalo–pelvic disproportion	1	4	1	1
Fetal distress	2	1	32	23
Antepartum haemorrhage	1	1	1	3
Abnormal lie	6	10	2	10
Previous Caesarean section	13	17	5	2
Multiple birth	0	1	0	0
Pre-eclamptic toxaemia	1	1	3	0
Placenta praevia	1	3	0	1
Other	6	2	0	1

TABLE IV. *Mean* (SD) *blood-gas data.* †$P < 0.01$; *$P < 0.05$ *between groups within same surgical category*

	Elective surgery		Emergency surgery	
	Group 50	Group 100	Group 50	Group 100
Umbilical vein				
pH	7.33 (0 03)	7 33 (0.03)	7.26 (0.11)	7.29 (0.06)
P_{CO_2} (kPa)	6.02 (0.64)	6 04 (0 71)	6.77 (1.66)	6.28 (1.06)
P_{O_2} (kPa)	4.89 (0 99)	5.84 (1.81)	4.00 (1.2)	5.01† (1.79)
Base deficit (mmol litre^{-1})	2.03 (1.35)	2.14 (1.87)	4.76 (4 88)	3.71 (2.65)
Umbilical artery				
pH	7.18 (0.04)	7.30 (0.06)	7.23 (0.12)	7.27 (0.08)
P_{CO_2} (kPa)	7.02 (7.59)	7.00 (0.73)	7.56 (1.52)	7.05 (1.09)
P_{O_2} (kPa)	3.12 (0 76)	3.06 (0.90)	3.06 (0.90)	2.73 (1.22)
Base deficit (mmol litre^{-1})	2.04 (0.97)	2.14 (2.14)	5.4 (5 89)	4.3 (4.19)
Arteriovenous difference (kPa)	1.67 (0.87)	2.83† (1.55)	1.29 (1.2)	2.11* (1.73)

difference was significantly greater in the 100% oxygen group for both elective and emergency sections ($P = 0.001$ and 0.004, respectively).

There was a tendency to higher Apgar scores at 1 min in group 100 for both elective and emergency sections, but this was not statistically significant (fig. 1); there was no difference between groups in 5-min Apgar scores.

There were no significant differences between groups in time to first breath and sustained ventilation (table V).

Babies born to mothers receiving 100% oxygen required more suction, but less oxygen and IPPV, immediately after delivery; requirement for intubation did not differ between groups (fig. 2). The smaller requirement for oxygen and IPPV after delivery in group 100 compared with group 50 was significant ($P < 0.05$) for all emergency

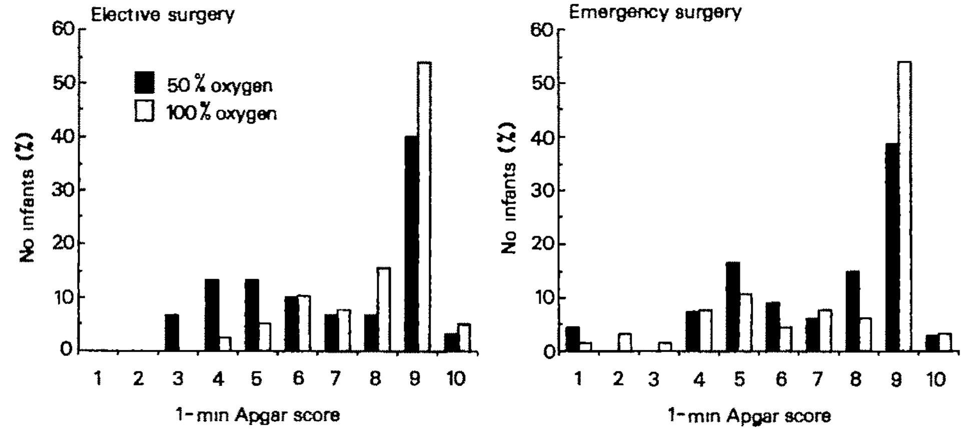

FIG. 1. One-minute Apgar scores of infants delivered by elective or emergency Caesarean section performed under isoflurane anaesthesia with 100 % or 50 % oxygen. No significant differences between groups.

TABLE V. *Time to first breath and sustained ventilation*

	Elective surgery		Emergency surgery	
	Group 50	Group 100	Group 50	Group 100
Time to first breath (s)	11 27 (24.1)	9 89 (17.2)	21.54 (48.4)	15 38 (57.4)
Time to sustained ventilation (s)	102 8 (101.3)	67.17 (70.8)	95.83 (83.5)	124 (197.9)

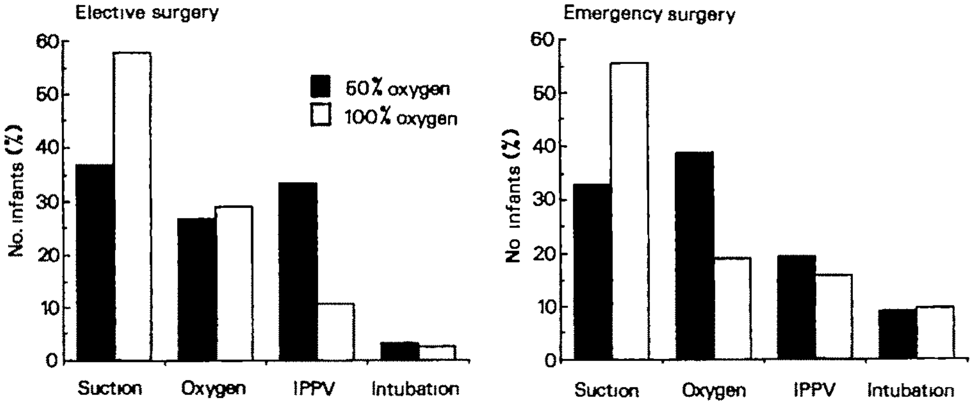

FIG. 2. Neonatal resuscitation of infants delivered by elective or emergency Caesarean section performed under isoflurane anaesthesia with 100 % or 50 % oxygen. The reduced requirement for oxygen in the emergency group is significant ($P < 0.05$).

patients considered together, but not in consideration of those elective and emergency deliveries performed for reasons other than fetal distress (fig. 3).

DISCUSSION

These results show that a greater umbilical venous $P\text{O}_2$ may be achieved by increasing the maternal inspired oxygen concentration to 100 %, particularly at emergency Caesarean section. Although the increase in oxygen tension may be small, the increase in oxygen content is substantial because of the greater oxygen affinity of fetal haemoglobin (at term accounting for 80 % of haemoglobin). The increase in oxygen tension in emergency cases would have greater implications for oxygen content, as it occurs on the steep portion of the oxygen dissociation curve.

These findings are in contrast with those of previous studies which suggested that a maternal $F\mathrm{I}_{\mathrm{O}_2}$ greater than 0.6 was of no benefit to fetal oxygenation. The design of these studies failed to control the depth of anaesthesia. Thus only 20% of the patients in Marx and Mateo's study [2] received an anaesthetic which provided greater than 1.0 MAC. Other patients had multiples of MAC between 0.52 and 0.62. Baraka [1] administered anaesthetics which provided multiples of MAC between 0.48 and 0.76. Moir [6] described a 4% incidence of recollection of painful events following anaesthesia for Caesarean section with 70% nitrous oxide in oxygen (0.64 × MAC). Awareness would therefore have been likely in these early trials, and the level of anaesthesia would have been unacceptably light, which may have resulted in increased plasma concentrations of catecholamines and placental vasoconstriction [7]. The same criticism may be levelled against the work of Rorke, Davey and DuToit [3], who used ether or methoxyflurane to achieve multiples of MAC greater than 1.0. The high blood-gas solubility of these agents would preclude them from being effective in the important interval between induction and delivery.

The need for resuscitation with oxygen was reduced significantly in the babies from the emergency group whose mothers received 100% oxygen. This finding paralleled the increase in umbilical vein $P\mathrm{O}_2$ and oxygen extraction and suggests that there is a clinical benefit. Administration of 100% oxygen did not seem advantageous in the elective group, and indeed there is evidence that a reduction in $F\mathrm{I}_{\mathrm{O}_2}$ from 0.5 to 0.3 in this group has no adverse effect on fetal oxygenation [8].

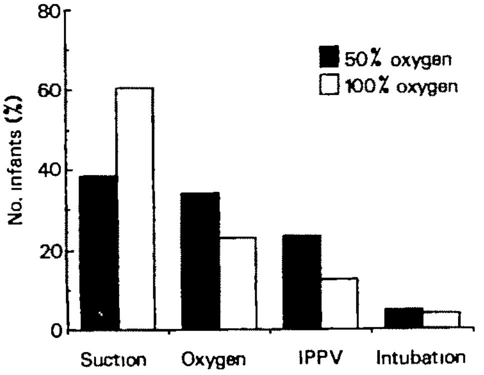

FIG. 3. Neonatal resuscitation of infants delivered by elective and emergency section, but excluding those with fetal distress. No significant difference between groups in requirement for oxygen.

The greater proportion of mothers in the 50% group whose deliveries were precipitated by fetal distress was a chance finding and it seems unlikely that this influenced the results. Analysis when the babies delivered because of fetal distress were excluded shows that there was still a reduction in neonatal resuscitation in group 100, although this was not statistically significant.

In the present study, the concentrations of isoflurane used were calculated to deliver equipotent anaesthetics in each group and, in addition, an isolated arm cuff permitted maternal movements so that the concentration of isoflurane could be increased. As in our previous study [4], the incidence of awareness was not increased in mothers receiving 100% oxygen, although the frequency of isolated arm movement was significantly higher. This lack of correlation is not surprising in view of the poor ability of the isolated arm technique to predict awareness [9].

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EXTRADURAL METHADONE AND BUPIVACAINE IN LABOUR

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SUMMARY

We performed a double-blind placebo-controlled study of the effects of extradural administration of methadone 5 mg or saline, followed by bupivacaine, in 42 women in early labour. Motor block and pain scores were significantly less in the methadone group. The requirement for bupivacaine also was reduced by methadone, but this was not statistically significant. There were no troublesome side effects attributable to methadone.

KEY WORDS

Anaesthesia obstetric extradural, methadone, bupivacaine

Extradural bupivacaine is the most effective method of providing analgesia for women in labour, but its use is associated with unwanted side effects. Sympathetic block is undesirable for both mother and fetus, and motor block may lead to an increase in the requirement for assisted delivery. In addition, the risk of systemic toxicity is present. The use of extradural opioids may avoid or reduce the adverse effects of the non-selective local anaesthetic agents.

Fentanyl, morphine and diamorphine have been given extradurally with some success, but are accompanied by complications, such as pruritus, which may be severe. Extradural administration of methadone for postoperative pain relief has been found to be effective and safe, with a duration of 5–8 h [1]. This study has assessed the effects of extradural administration of methadone 5 mg to primigravid patients in early labour.

PATIENTS AND METHODS

We studied 42 patients in early labour who had requested extradural analgesia. Those who had progressed beyond cervical dilatation of 4 cm or had already received an opioid were excluded. Informed consent was obtained from participants and the study was approved by the Hospital Ethics Committee.

The extradural space was identified at the L2–3 or L3–4 interspace and a catheter inserted. The patients were allocated randomly to receive methadone or saline. The solutions were prepared and coded by a second investigator and injected by an anaesthetist who was unaware of the identity of the solution. Patients in group 1 received normal saline 10 ml and those in group 2 received preservative-free methadone 5 mg in normal saline 10 ml. If pain relief was unsatisfactory, the time was noted and the patients were given a test dose of 0.25% bupivacaine plain solution 3 ml followed, in the absence of complications, by a further 5–7 ml. Subsequent top-ups of 0.25% bupivacaine were given on demand by midwives, following routine practice in the Queen Mother's Hospital.

The investigator unaware of the solution given recorded the age, weight, height and cervical dilatation for each patient and undertook subsequent neurological assessments. Pain was assessed using a 10-cm visual analogue scale before insertion of the extradural catheter, for overall pain during labour and for pain at delivery. The level of sensory block was assessed at 2-h intervals, using loss of sensation to ice. Motor

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block was graded at the same intervals as: grade 0 = no weakness; grade 1 = able to raise a straight leg; grade 2 = able to flex knee; grade 3 = unable to flex knee.

The doses and times of subsequent top-up doses of bupivacaine were recorded, as were the neonatal Apgar scores at 1 and 5 min. The complications of hypotension (SAP < 100 mm Hg), nausea, vomiting and pruritus were noted if they occurred. The duration of the second stage, the need for catheterization of the bladder and the occurrence of sacral pain or rectal pressure were noted also.

Statistical analysis was with Mann–Whitney *U* and chi-square tests where appropriate. $P < 0.05$ was considered statistically significant.

TABLE II. *Requirements for bupivacaine in both groups* *P < *0.05 between groups*

	Group 1 (control)		Group 2 (methadone)
Total dose (mg)			
Mean	103.6		77.6
Median	80		70
Range	45–272		32.5–210
Rate (mg h^{-1})			
Mean	16 7		13 2
Median	12.3		13 8
Range	6.3–22		8–38
Time to first bupivacaine top-up (min) (mean (SD))	17.3 (11)	*	33.5 (33)

TABLE III. *Number of patients with various grades of motor block.* *P < *0.05 between groups*

Grade of block	Group 1 (control)		Group 2 (methadone)
0 = No weakness	0		0
1 = Able to raise straight leg	5		10
2 = Able to flex knee	6		8
3 = Unable to flex knee	5	*	0

RESULTS

The two groups were comparable for age, weight, height, cervical dilatation and pain score before insertion of the extradural catheter (table I). Forty-two patients were recruited into the study.

Four patients were excluded from further study because delivery took place within 2 h of insertion of the extradural catheter. One patient was excluded after accidental dural puncture before injection of the trial solution, and another after failure to follow the programme, leaving 17 patients in group 1 and 18 in group 2.

The time interval from injection of the trial solution to the first dose of bupivacaine was significantly longer in group 2. The mean and median rates of administration of bupivacaine and the total dose were also less in group 2, but this was not statistically significant (table II). There was no significant difference in the number of subsequent top-ups required.

The median pain score for overall pain during labour was 3.16 in the control group (range 0–7) compared with 1.45 in the methadone group (range 0–4.7) ($P < 0.01$). The incidence of rectal pressure and pain score at the time of delivery were similar in the two groups.

TABLE I. *Patient data (mean (SD) or median (range))*

	Group 1 (control) ($n = 17$)	Group 2 (methadone) ($n = 18$)
Age (yr)	25.4 (3 98)	26.8 (6.3)
Height (m)	1.62 (0.065)	1.61 (0 074)
Weight (kg)	72.2 (9.94)	71.7 (9.08)
Pain score before catheter insertion (cm)	7.2 (1.0–10)	7.4 (3.8–9.6)

Both groups were affected by motor block, but five patients in the control group developed grade 3 motor block, compared with none in the methadone group (table III). This was significant ($P < 0.05$), reflecting the greater dose of bupivacaine in the control group.

There were no significant differences between the groups in the incidence of nausea and vomiting. There were no instances of respiratory depression. Four patients in the control group developed hypotension; all responded to an increase in the rate of i.v. infusion. Four patients in the methadone group experienced mild itching, but this was elicited only by direct questioning and was not troublesome. One of these mothers had suffered from itch throughout pregnancy. There were no significant differences between the groups in neonatal Apgar scores or in the requirement for assisted delivery with either forceps or vacuum extraction. The need for bladder catheterization was significantly less in the methadone group.

DISCUSSION

This study has shown that methadone 5 mg administered extradurally in labour did not reduce significantly the requirement for bupivacaine administered subsequently. However, significant reductions were found in both pain and motor block in the methadone group.

Early reports indicated that both intrathecal and extradural morphine produced analgesia which was effective in the management of severe pain. However, the introduction of extradural opioids to obstetric practice was disappointing. Extradural morphine 2–6 mg was found to be unsatisfactory in relieving the pain of labour [2–4]. Increasing the dose to 7.5 mg was found to give satisfactory analgesia in some patients during labour, but supplementation with bupivacaine was required at delivery [5]. Similarly, extradural fentanyl 150–200 µg produced analgesia until late in the first stage of labour [6]. In this study the longer time to the first dose of bupivacaine in the methadone group indicates that patients obtained analgesia from methadone alone, but bupivacaine was required to produce adequate analgesia in all patients.

More promise has been shown in studies which combined an opioid with local anaesthetic. Fentanyl with bupivacaine produced more rapid and complete analgesia than bupivacaine alone [7–10]. Extradural diamorphine 5 mg has been shown to reduce requirement for bupivacaine, pain scores and motor block in labour, but itching proved troublesome and occasionally required treatment with naloxone [11].

The pharmacokinetics of drugs administered into the extradural space are altered in pregnancy. Obstruction of the inferior vena cava may cause distension of the extradural veins and increased flow through the azygos vein. This results in more rapid absorption of opioid from the extradural space, leaving less drug available for transfer across the dura to the spinal cord [12]. This may limit the efficacy of the extradural methadone technique in labour.

Late onset respiratory depression has been observed in patients given extradural opioids, particularly morphine. The uptake of morphine into the spinal cord is slow, as it is poorly lipid soluble and remains in the cerebrospinal fluid and migrates cephalad [13]. More lipid soluble drugs, such as methadone and fentanyl, have not been reported to cause late onset respiratory depression when used in appropriate doses. Therefore, methadone would appear to be a more suitable and potentially safer agent than morphine. However, when used as described, methadone required addition of bupivacaine to provide adequate analgesia. Analgesia was then superior to that produced by bupivacaine alone and muscle weakness was reduced.

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PLASMA CONCENTRATIONS OF THE STEREOISOMERS OF PRILOCAINE AFTER ADMINISTRATION OF THE RACEMATE: IMPLICATIONS FOR TOXICITY?†

G. T. TUCKER, L. E. MATHER, M. S. LENNARD AND A. GREGORY

SUMMARY

A chiral high pressure liquid chromatography method was developed to measure the separate isomers of prilocaine in plasma after administration of the racemate. The concentrations of the isomers in six patients were similar (S(+)/R(−) = 1.06 (SD 0.06)) after brachial plexus block with 1.5% (RS)-prilocaine hydrochloride 35 ml, suggesting that a higher systemic safety margin may not be achieved by substituting racemic prilocaine by one of its isomers. Much higher plasma concentrations of the S(+)- than the R(−)-form after oral administration of 300 mg of the racemate (n = 4) indicated a large difference in intrinsic metabolic clearance of the isomers on first pass through gut, liver or both organs.

KEY WORDS

Anaesthetics, local: prilocaine. Toxicity: local anaesthetics.

(RS)-Prilocaine (α-propylamino-2-methylpropionanilide) is considered to be the local anaesthetic of choice for i.v. regional anaesthesia and brachial plexus block, as it has a relatively low potential for systemic CNS toxicity because of rapid blood clearance (2.4 litre min^{-1}) by both hepatic and extrahepatic metabolism [1, 2]. However, its use is limited essentially to single injection procedures because metabolism by amide hydrolysis and hydroxylation of the toluidine product is associated with methaemoglobinaemia [3]. Unlike lignocaine, which does not exhibit optical isomerism, but in common with other clinically used amide-type agents, prilocaine is given as a racemate (a 50:50 mixture of both isomers). Therefore, as the ratio of the intrinsic anaesthetic activities of the enantiomers is small [4], the possibility of stereoselective metabolism might suggest a further advantage with respect to systemic safety in using a single isomer. To investigate this, a method was developed to measure the separate plasma concentrations of S(+)- and R(−)-prilocaine by chiral column high pressure liquid chromatography (HPLC) after administration of the racemate.

PATIENTS AND METHODS

Brachial plexus block was performed on six surgical patients using (RS)-prilocaine hydrochloride 525 mg (35 ml of 1.5% solution). These patients formed part of a larger study of the influence of different techniques of brachial plexus block on the systemic absorption of prilocaine, which was described in detail by Maclean and colleagues [5]. In addition, four healthy male anaesthetists received (RS)-prilocaine hydrochloride 300 mg by mouth as an aqueous solution. Both studies were approved by the local Ethics Committee. The latter study was included to assess the relative intrinsic metabolism of the isomers uncomplicated by the influence of blood flow on clearance. Serial venous blood samples were taken up to 60 min after brachial plexus injection and up to 120 min after the oral dose.

Plasma concentrations of unresolved drug were measured by gas–liquid chromatography (GLC). Alkalinized plasma 1.0 ml containing internal standard (ethylmethylglycinexylidide)

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was extracted with diethylether 5 ml, followed by back-extraction into 200 µl of hydrochloric acid 1 mol litre^{-1}. This was then alkalinized and extracted with cyclohexane 40 µl, 5–10 µl of which was injected into the gas chromatograph. An OV-225 column (2 m × 4 mm i.d.) was used together with a nitrogen detector. The lower limit of this method was 50 ng ml^{-1}, at which concentration the intra-assay coefficient of variation was 7% (n = 10).

The ratio of the isomers was estimated using a 4.6-mm i.d. × 250-mm HPLC column containing cellulose tris-3,5-dimethylphenyl carbamate coated on silica gel (Chiralcel OD; Daicel Chemical Industries Ltd), after extracting the compounds from alkalinized plasma 0.5 ml into n-hexane 300 µl. The column was eluted with n-hexane:3-propanol:diethylamine (80:20:0.01) at a flow rate of 1 ml min^{-1}, and u.v. detection was at 263 nm. Powdered (RS)-prilocaine hydrochloride and the commercial solution for injection were used as standards to assess the relative concentrations of the isomers in plasma samples. Thus isomer ratios in the latter were compared with those found after extraction of blank plasma spiked with comparable concentrations of the standards. The isomer ratio was measured with a precision of ±4% at concentrations of individual isomers down to 50 ng ml^{-1}. It was not possible to assay the concentrations of each isomer directly using the chiral column because a suitable internal standard was not found.

Maximum values of plasma drug concentrations (*C*max) were noted and areas under the plasma drug concentration–time curves (AUC) to the last datum point were estimated using the linear trapezoidal rule. Differences between the values observed for the two isomers were evaluated using Student's paired t test, assuming significance at $P < 0.05$.

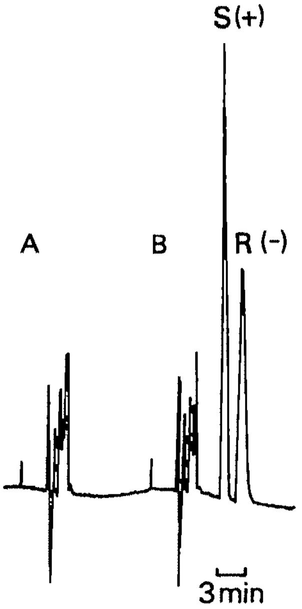

FIG. 1. Chiral high pressure liquid chromatograms of extracts from A: blank plasma; B: plasma from a patient after injection of (RS)-prilocaine for brachial plexus block (S(+)- 1.59 µg ml^{-1}; R(−)- 1.15 µg ml^{-1}). 0.01 absorbance units, full scale deflection.

RESULTS

Complete baseline separation of the isomers was achieved using the chiral column, with retention times of 6.8 min for S(+)- and 8.2 min for R(−)-prilocaine (fig. 1). The column proved to be robust, although the guard-column containing the same material had to be replaced after 500 injections. Prilocaine was stable in frozen plasma and there was no evidence of a change in isomer ratios or inversion of the isomers on prolonged storage. Isomer ratios in samples spiked with the standards were independent of total racemic drug concentration over the working range, and there was no difference in the ratio as a function of the source of the standard (powder or solution for injection).

Mean plasma concentrations of the individual isomers after the two routes of administration of the racemate are shown in figure 2. Concentrations of the R(−)- isomer after oral administration of (RS)-prilocaine were very low and below the limit of assay at most time points in all subjects. Mean (SD) values of AUC(0, 60 min) and *C*max following brachial plexus injection were 43 (15) µg ml^{-1} min and 1023 (352) ng ml^{-1} for S(+)-prilocaine and 41 (17) µg ml^{-1} min and 990 (381) ng ml^{-1} for R(−)-prilocaine. The differences between the isomers were statistically significant (paired test, $P < 0.05$). After oral administration AUC(0, 120 min) and *C*max values were 9.2 (2.4) µg ml^{-1} min and 157 (81) ng ml^{-1}, respectively for S(+)-prilocaine, but could not be estimated accurately for the R(−)-isomer. The average S(+):R(−) ratio for all samples in each patient after brachial plexus injection was 1.06 (0.06), with no evidence of a change with time. In contrast, after oral administration plasma

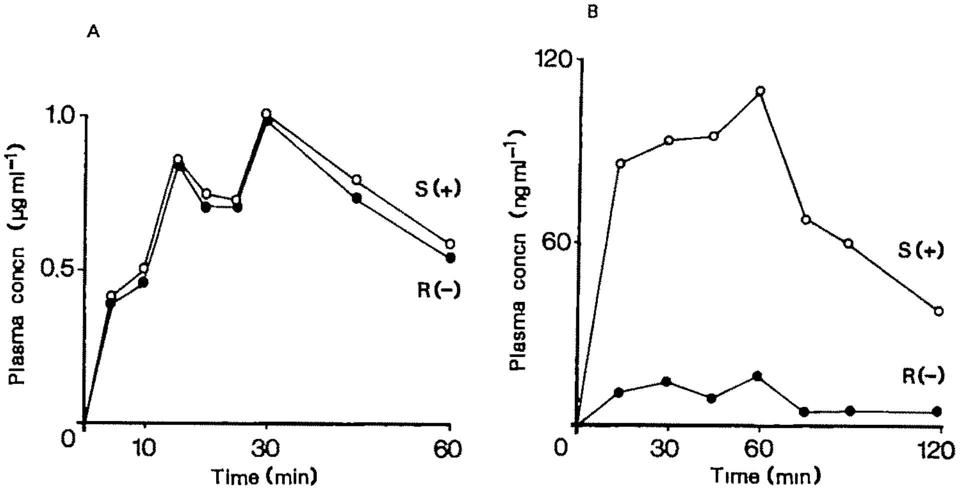

FIG. 2. Mean venous plasma concentrations of the enantiomers of prilocaine after A: brachial plexus block with racemic prilocaine hydrochloride 525 mg (35 ml of 1.5% solution) ($n = 6$); B: oral administration of racemic prilocaine hydrochloride 300 mg ($n = 4$). Note the differences in scales. Concentrations of the R(−)-isomer after oral administration of the racemate were detectable in most samples, but below the limit of confident assay.

concentrations of S(+)- drug were at least eight times greater than those of the R(−)-isomer. Values of the time to *Cmax* were in the range 15–60 min following both routes of drug administration.

DISCUSSION

The marked route-dependence of the plasma S:R ratio may be explained by blood flow-limited systemic clearance of both isomers after parenteral injection, and an appreciable first-pass effect after oral administration manifesting a large difference in the intrinsic metabolic clearance of the antipodes. Thus theory predicts that the kinetics of a drug with a high hepatic clearance should be blood flow-dependent after parenteral administration, but dependent largely upon enzyme activity after oral administration [6]. In addition, stereoselective presystemic metabolism within the gut wall might contribute to the large difference in plasma concentrations of the isomers after oral administration. Any difference in the plasma binding of the isomers would contribute also to the differences seen in their total plasma concentrations. However, such a difference would not be route-dependent and the extent of binding of prilocaine is relatively low [7]. Assuming that absorption is a passive process, a difference in the relative absorption rate of the isomers from the site of administration cannot account for the observations, as enantiomers have identical physico-chemical properties. Furthermore, any stereoselectivity of their effects on local blood flow would not influence relative absorption rate when the isomers are given together as a racemate.

As the isomers of prilocaine show little differences from the racemate in their anaesthetic effect and in their i.v. LD_{50} values in animals [4, 8], and we have shown that their plasma concentrations after perineural injection of the racemate are similar in man, this supports the view that a higher safety margin for systemic CNS toxicity may not be achieved by substituting racemic prilocaine by one of its isomers. A caveat to this is that a slower systemic uptake of one isomer, as a result of differential effects on local blood flow, could recommend it over the racemate. Such differences have been observed in animals [4], but they appear to be relatively minor.

A further issue is that, if significantly smaller plasma concentrations of one isomer had been shown following perineural injection, this would have to be set against the possibility of more rapid formation of the metabolic products responsible for methaemoglobinaemia. Thus Akerman and Ross [4] observed smaller plasma concentrations of R(−)-prilocaine after i.v. injection of the separate isomers into cats, but the rate of production of methaemoglobin was correspondingly faster. It should be noted that several authors have misrepresented this work in proposing prilocaine as an example of the clinical use of a single isomer being preferred over the racemate. Thus it has been claimed that only the R(−)-isomer undergoes metabolic hydrolysis to toluidine and hence produces methaemoglobinaemia [9–11]. The original work notes merely a difference in the rate and not the extent of methaemoglobin formation after administration of the isomers [4].

The abolition of the centre of asymmetry in prilocaine by addition of another methyl group, to produce quatacaine, is claimed to obviate the problem of methaemoglobinaemia while retaining the anaesthetic profile [11, 12]. However, this change is at the expense of increased CNS toxicity, probably as a result of protecting the amide linkage against rapid hydrolysis. It remains difficult to see how the structure of prilocaine might be modified to lower the propensity for methaemoglobin formation, while retaining the high systemic clearance and safety margin with respect to CNS toxicity.

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DIURETICS AFTER TRANSURETHRAL PROSTATECTOMY: A DOUBLE-BLIND CONTROLLED TRIAL COMPARING FRUSEMIDE AND MANNITOL

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AND D. G. KELLY

SUMMARY

Mannitol and frusemide were compared in a randomized, controlled, double-blind trial for their effects in promoting diuresis after prostatectomy and on indices of water intoxication. The drugs had comparable diuretic effects. Sodium loss was greater with frusemide, contributing to sodium depletion after operation. Administration of frusemide was associated with more frequent need for i.v. volume expansion after operation. Plasma osmolality was greater with mannitol (289 (SD 4.2 mosmol kg^{-1} at 1 h after operation and 285 (5.3) mosmol kg^{-1} at 4 h after operation) than with frusemide (282 (7.1) mosmol kg^{-1} and 279 (6.7) mosmol kg^{-1}, respectively) ($P < 0.05$). Plasma concentration of sodium was significantly greater with mannitol (136.9 (3.1) mmol litre^{-1}) than with frusemide (134.4 (2.8) mmol litre^{-1}) only on the morning after surgery ($P < 0.05$). Mannitol is an effective alternative to frusemide in inducing diuresis after prostatectomy, and may protect against water intoxication.

KEY WORDS
Kidney, diuretics. frusemide, mannitol, water intoxication. Surgery: prostatectomy.

Uptake of water from irrigating fluid via open venous sinuses in the prostatic bed results in dilutional hyponatraemia and hypo-osmolality in the transurethral prostatectomy (TURP) syndrome. Hyponatraemia and hypo-osmolality cause CNS disturbances (drowsiness, confusion, convulsions and pontine myelinolysis if severe) [1]. The incidence of this complication is reported to be 2–10% [2, 3].

Frusemide is a loop diuretic used commonly after prostatectomy to promote diuresis, reducing the risk of clot retention. Mannitol, an osmotic diuretic, causes primarily water excretion by the kidney [4, 5]. This study was undertaken to compare the effects of mannitol and frusemide on sodium and water excretion after transurethral prostatectomy, and their ability to influence the development of the TURP syndrome.

PATIENTS AND METHODS

We studied patients undergoing TURP under spinal anaesthesia. Informed consent was obtained from each patient. A pilot study of 10 patients was undertaken, after which the dose of mannitol was altered, followed by a study of 30 patients receiving either frusemide or mannitol after prostatectomy, and a study of five patients given mannitol *during* prostatic resection. Diabetic subjects (5% glucose was used as the carrier for frusemide) and patients unsuitable for spinal anaesthesia were excluded from the study.

All long term medications were given on the morning of surgery. Three patients in the mannitol group and one patient in the frusemide group were receiving long term diuretics, which were given on the morning of surgery. Diazepam

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10 mg was given orally 2 h before operation; no additional sedation was given during surgery. Hartmann's solution 10 ml kg^{-1} was used for i.v. volume loading before spinal anaesthesia, and additional Hartmann's solution was infused during prostatic resection to maintain the systolic arterial pressure > 100 mm Hg; no significant hypotension was encountered during the operation. Spinal anaesthesia was produced with 0.5% bupivacaine 3.5 ml. A 16-gauge i.v. cannula was inserted for blood sampling in the antecubital fossa opposite to the i.v. infusion.

Diuretic therapy

At the *end* of prostatic resection, patients were allocated randomly to receive an i.v. infusion, over 10 min, of either frusemide or mannitol. The infusions were constituted in identical bottles with coded labels: randomization was by opening a sealed envelope, assigning the code-word of an infusion. Patients and investigators were blinded to the diuretic used.

In the pilot study, frusemide 40 mg (in 200 ml of 5% glucose) was compared with mannitol 40 g (200 ml of a 20% solution). In the main study frusemide 40 mg (in 400 ml of 5% glucose) and mannitol 80 g (400 ml of a 20% solution) were compared. In all cases the infusions were given over 10 min.

After completion of the diuretic infusion the patients received a standardized i.v. fluid regimen of 0.9% sodium chloride 80 ml h^{-1} for the first 24 h after operation. Patients were encouraged to take oral fluids on the evening of surgery.

Age, body weight, total volume of i.v. fluid infused during operation (from preload before spinal anaesthesia to end of resection), oral intake in the first 12 h after operation, duration of prostatic resection and weight of gland resected were recorded. Urine output was measured every 1 h after operation. Patients were observed for confusion, drowsiness, agitation and changes in arterial pressure.

Blood samples for measurement of sodium concentration and osmolality were taken before operation, at the end of prostatic resection (before diuretic), 1 and 4 h after surgery, and the following morning. Urine samples for measurement of osmolality were taken before operation, 1 and 4 h after surgery, and the following morning. Plasma and urine [Na^+] were measured using flame photometry, and osmolality by depression of freezing point using a Fiske osmometer.

Statistical analysis

Data were subjected to goodness of fit tests to confirm normal distribution. Demographic data were compared using unpaired Student's *t* tests. Data comparing preoperative and postoperative biochemistry within each group were analysed using paired Student's *t* tests; differences between groups were compared using unpaired Student's *t* tests. "*V* square" (Chi-squared test with correction for sample size) tests were used to compare non-parametric data (incidence of symptoms and complications) [6]. $P < 0.05$ was taken as significant. Values are expressed as mean (SD).

RESULTS

Pilot study

Ten patients were studied: five received mannitol 40 g and five frusemide 40 mg. The mean urine output in the first 1 h after operation was 186 (123) ml in the mannitol group and 387 (288) ml in the frusemide group. No untoward effects were noted. Because of the lesser urine output, the dose of mannitol was doubled to 80 g for the main study. Unless stated otherwise, all subsequent data refer to the main study.

Main study

Fifteen patients received frusemide 40 mg and 15 received mannitol 80 g, at the end of prostatic resection. There were no differences between the two groups as regards age, weight, duration of prostatic resection, mass of gland resected, volume of i.v. fluid administered during the operation and oral intake after operation (table I).

Urine volume

Urine output was measured in 11 patients in each group: the other patients required con-

TABLE I. *Patients, operations and details of fluid intake (mean* (SD)). *No significant differences between groups*

	Mannitol ($n = 15$)	Frusemide ($n = 15$)
Age (yr)	73.0 (4.8)	73.5 (7 6)
Weight (kg)	72.2 (9.6)	71.4 (9.2)
Plasma urea (mmol $litre^{-1}$)	7.37 (2.0)	7 4 (2.2)
Resection time (min)	28 7 (13.2)	31.0 (16.3)
Gland resected (g)	25 6 (25.9)	25.4 (18.7)
I.v. fluids during op. (ml)	1246 (479)	1073 (262)
Oral intake first 12 h after op. (ml)	998.7 (576)	1057 (261)

TABLE II. MEAN (SD) *hourly urine output, hourly urinary excretion of sodium, plasma osmolality and plasma sodium concentration, according to diuretic used. Significant differences between groups:* *$P < 0.05$; ** $P < 0.005$; *** $P < 0.001$

	Mannitol		Frusemide
Urine output (ml h^{-1})			
($n = 11$)			
0–1 h	688 (519)	*	910 (672)
1–2 h	200 (187)		365 (326)
2–3 h	193 (170)		293 (241)
3–4 h	198 (181)		270 (198)
5–9 h	149 (90)		131 (70)
10–13 h	138 (86)		119 (68)
Sodium excretion (mmol h^{-1})			
($n = 11$)			
1 h after op.	41.1 (5.6)	***	82.6 (27.7)
4 h after op.	12.9 (8.5)	***	26 1 (7.2)
Next a.m.	9.1 (2.5)		9.6 (4.7)
Plasma osmolality (mosmol kg^{-1})			
($n = 15$)			
Preop.	283 (4.0)		285 (6.4)
End resection	282 (5.1)		283 (6.8)
1 h after op.	289 (4.2)	**	282 (7.1)
4 h after op.	285 (5.3)	*	279 (6.7)
Next a.m.	279 (6.0)		277 (7.9)
Plasma sodium (mmol $litre^{-1}$)			
($n = 15$)			
Preop.	139.8 (2.5)		138.5 (2.4)
End resection	137.2 (3.1)		134.0 (8.4)
1 h after op.	132 6 (3.6)		132.9 (7.2)
4 h after op.	135.5 (3.2)		134.2 (5.8)
Next a.m.	136.9 (3.1)	*	134.4 (2 8)

tinuous irrigation of the bladder after operation because of bleeding, rendering assessment of urine output impossible. Measured urine output was significantly greater in the first 1 h after operation in patients who received frusemide ($P < 0.05$); thereafter volumes were similar for each group (table II).

Urinary excretion of sodium

Urinary excretion of sodium was less in the mannitol group than in the frusemide group at both 1 and 4 h after operation. By the following morning the groups were similar (table II).

Plasma osmolality

The mannitol group had significantly greater plasma osmolality at 1 and 4 h after operation (table II). There was an increase in plasma osmolality with administration of mannitol (at 1 h after operation compared with the end of resection ($P < 0.05$)), whereas administration of frusemide was associated with a decrease in plasma osmolality (at 4 h compared with the end of resection ($P < 0.05$)). Both groups showed decreases in plasma osmolality by the next morning compared with the end of resection ($P < 0.05$). The range of plasma osmolality was 269–298 mosmol kg^{-1} (normal range 275–295 mosmol kg^{-1}).

Plasma concentration of sodium

Both groups showed decreases in plasma sodium concentration at 1 h, 4 h and the morning following surgery compared with before operation ($P < 0.05$). On the morning following surgery, the mannitol group had a plasma concentration of sodium significantly greater than that in the frusemide group (table II). The range of plasma concentration of sodium was 112–143 mmol $litre^{-1}$.

Symptoms and complications

Thirst in the postoperative period was volunteered significantly more frequently in the mannitol group (seven given mannitol, two given frusemide) ($P < 0.05$).

There was no statistical difference between the groups in the incidence of confusion, drowsiness or agitation (one patient given mannitol, four given frusemide). The mean value for lowest plasma concentration of sodium was 124.8 (10.4) mmol $litre^{-1}$ for patients with CNS symptoms, compared with 133.4 (3.5) mmol $litre^{-1}$ for those without ($P < 0.05$).

One patient in the mannitol group and two in the frusemide group received blood transfusions because of bleeding. Increased i.v. fluid was given when clinical evidence suggested hypovolaemia in the immediate postoperative period (hypotension, syncope, cold periphery); this was necessary in two patients who received mannitol compared with seven patients who received frusemide ($P < 0.05$).

Administration of mannitol during prostatic resection

Mannitol 80 g given *during* prostatic resection to five patients increased plasma osmolality during surgery (from 284 (6.3) mosmol kg^{-1} to 290 (3.8) mosmol kg^{-1}) ($P < 0.05$), which was similar to the change when mannitol was given after operation.

DISCUSSION

The TURP syndrome varies in severity from drowsiness and confusion, to coma, convulsions and pontine myelinolysis [3]. Diuretic therapy is intended primarily to prevent bladder clot retention after TURP, but may aggravate or ameliorate the TURP syndrome.

Both mannitol 80 g and frusemide 40 mg were effective in promoting diuresis after prostatectomy. Urine output in the first 1 h was less (but "adequate") with mannitol and could be overcome by administration during surgery.

Frusemide induces a sodium diuresis, in contrast with the relatively sodium-sparing osmotic diuretic, mannitol [4, 5]. Sodium depletion consequent on the natriuresis may precipitate hypovolaemia. Mannitol 20% is a hypertonic solution and would be expected to increase extracellular volume [7]. Previous studies have documented a transient expansion in blood volume, returning to normal after 30 min [8]. This contrasts with the tendency to hypovolaemia with frusemide and is consistent with the greater incidence of clinically suspected hypovolaemia seen with frusemide in the immediate postoperative period of this study. However, caution is needed in interpreting these findings, as blood loss was not quantified and decisions to transfuse blood or increase i.v. fluids were made only on clinical grounds.

This study confined itself to the water intoxication component of the TURP syndrome as identified by its biochemical hallmarks: hyponatraemia and hypo-osmolality. In a study of this size, significant differences in the incidence of clinical CNS disturbances would be unlikely. However, the results suggest that mannitol might reduce the incidence of CNS disturbances after TURP. CNS disturbances may also follow glycine intoxication, which can occur independently of the degree of water intoxication [9].

The small changes in mean plasma sodium concentration for the groups as a whole (138.5 to 132.9 mmol litre^{-1} with frusemide) hide the magnitude of changes in individual subjects. For example, two patients receiving frusemide had reductions in plasma concentration of sodium from 140 and 136 mmol litre^{-1} to 115 and 112 mmol litre^{-1}, respectively, with associated CNS changes. As sodium chloride is the principal solute of the extracellular space, hyponatraemia is *usually* indicative of hypo-osmolality; in pure water intoxication this is reliable, but not if an extra solute is present. In the presence of high concentrations of mannitol, extreme hyponatraemia ([Na$^+$] 99 mmol litre^{-1}) with *normal* plasma osmolality has been reported, with no CNS effects of water intoxication [10]. We suggest that hypo-osmolality is a more appropriate marker of water intoxication than hyponatraemia.

Mannitol has an established role in treating water intoxication by drawing water from the intracellular space, reducing brain oedema, and increasing urinary water loss [11]. A slow infusion of mannitol during surgery is preferable to prevent hypo-osmolality. Central pontine myelinolysis has been linked to rapid correction of hypo-osmolality [1, 12]. Likewise, commencing the diuresis during the operation should also ensure adequate urine flow during the first minutes after operation—the most crucial time in the prevention of clot retention.

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DOMICILIARY OXYGEN CONCENTRATORS IN ANAESTHESIA: PREOXYGENATION TECHNIQUES AND INSPIRED OXYGEN CONCENTRATIONS

I. H. WILSON, P. V. VAN HEERDEN AND J. LEIGH

SUMMARY

A conventional preoxygenation technique was compared in two volunteers with two techniques based on a drawover breathing system supplied with oxygen enriched air from a Devilbiss Mini VO2 domiciliary oxygen concentrator. Breathing from a 20-litre bag, filled previously at 2 litre min^{-1} from the concentrator was as effective as the conventional technique (Pa_{O_2} *73.2 kPa). Supplying 4 litre min^{-1} to a drawover system was less effective (*Pa_{O_2} *35.5 kPa). We present a simple method for determining the inspired oxygen concentration obtained under conditions of drawover anaesthesia using an oxygen concentrator.*

KEY WORDS
Anaesthetic techniques: drawover apparatus, preoxygenation. Equipment: oxygen concentrator.

Oxygen concentrators are capable of separating oxygen from other atmospheric gases by filtration through zeolite columns which act as molecular sieves [1]. Concentrators of varying capacity are available, the most common being the electrically powered "domiciliary oxygen concentrator" used for oxygen therapy at home. The use of these devices has been investigated for oxygen supplementation during drawover anaesthesia [2–4]. Small size and portability make them an ideal oxygen source for use in situations in which there are shortages of compressed gases, such as military and disaster situations or developing countries [5, 6]. In addition, considerable financial savings may result from reduced cylinder hire and transportation costs, as has been shown recently in Malawi, where all government hospitals use concentrators in theatres as the main supply of oxygen [6].

The oxygen concentration delivered by a concentrator depends on the model used and on the flowmeter setting. At low flow rates, the oxygen is highly concentrated, but at higher flow rates the oxygen is less concentrated, as the nitrogen absorption by zeolite becomes less efficient. A typical domiciliary oxygen concentrator produces approximately 2 litre min^{-1} of 95% oxygen or 4 litre min^{-1} of 70–80% oxygen, the balance being nitrogen and argon [1].

During anaesthesia there are times when a high flow of oxygen is required, most commonly for preoxygenation [7]. This process is difficult when a domiciliary oxygen concentrator is used as the oxygen source in a drawover circuit, as the limited flow of oxygen provided allows air to be drawn into the circuit, diluting the oxygen. This results in inefficient preoxygenation, particularly in patients who are hyperventilating.

Two methods may be used for preoxygenation when using an oxygen concentrator. The method practised most commonly involves breathing through a standard drawover circuit [8] with a flow of 4 litre min^{-1} of concentrator "oxygen" added to the circuit via a T-piece. Some workers recommend adding to the circuit a larger reservoir which has been pre-filled with concentrator "oxygen" [9].

During use of the concentrator, the inspired oxygen concentration depends on concentrator flow and ventilatory volume. We studied the effect of these variables on the inspired concentration of oxygen and assessed the efficiency of preoxygenation under conditions of drawover anaesthesia.

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SUBJECTS AND METHODS

A Devilbiss Mini VO2 oxygen concentrator, the output of which had been confirmed to be within manufacturer's recommendations using a calibrated gas analyser (Datex Normocap), was used. Between experiments using different concentrator flow rates, adequate time was allowed for the output of the concentrator to stabilize as judged by gas analysis.

Two techniques of preoxygenation using an oxygen concentrator were compared with a standard method using a Magill circuit in two of the authors (ASA I, age 29 and 33 yr, weight 78 and 73 kg) who had been subjected to arterial cannulation to facilitate blood-gas analysis. During each of the techniques of preoxygenation, blood was drawn during the final 5 s and was analysed immediately using an Instrumentation Laboratories 1312 blood-gas analyser. Subjects breathed atmospheric air between experiments for at least 10 min, to allow alveolar gases to normalize. Three baseline blood-gas samples were obtained with the subject breathing air and analysed for comparison. Three techniques were evaluated:

Magill technique. The subject breathed for 3 min from a Boyle's machine via a standard Magill circuit with a flow of oxygen 6 litre min^{-1}. The reservoir bag was filled with oxygen at the start of the experiment.

Standard drawover technique. Using the circuit illustrated in figure 1, 4 litre min^{-1} of concentrator "oxygen" was added to a standard drawover circuit which comprised an Ambu E valve, T-piece for oxygen addition and a 1-litre reservoir tube. We assessed the efficacy of preoxygenation at a minute ventilation of 10 litre min^{-1}. To facilitate this we added air 6 litre min^{-1} via a 2-litre reservoir bag which was connected to the circuit as shown in figure 1. At the start of preoxygenation, the reservoir tubing was filled with concentrator gas, the reservoir bag was empty and the air flow was started as the subject was connected to the circuit. After 3 min of preoxygenation, blood was drawn for analysis during the final 5 s. During the experiment the subject breathed so as to keep the reservoir bag between empty and half full.

Drawover technique with a 20-litre reservoir. A 20-litre reservoir bag (made from a disposable plastic bag), pre-filled from the output of the concentrator at 2 litre min^{-1}, was connected directly to the inlet port of the Ambu E valve. The subject breathed from the reservoir until it was empty and a blood sample was taken during the last breath. The time taken to empty the bag was noted.

Each subject performed the three techniques on three separate occasions.

We calculated the inspired oxygen concentration during drawover anaesthesia in relation to patient ventilation when a domiciliary oxygen concentrator is used, applying the formula:

$$F\mathrm{I}_{\mathrm{O}_2} = \frac{0.21(\dot{V}\mathrm{E} - \dot{V}\mathrm{C}) + (\dot{V}\mathrm{C} \times F\mathrm{C}_{\mathrm{O}_2})}{\dot{V}\mathrm{E}}$$

where $F\mathrm{I}_{\mathrm{O}_2}$ = fractional inspired oxygen concentration; $F\mathrm{C}_{\mathrm{O}_2}$ = fractional oxygen delivered by concentrator; $\dot{V}\mathrm{E}$ = minute ventilation (litre min^{-1}); $\dot{V}\mathrm{C}$ = concentrator flow (litre min^{-1}).

Data were subjected to analysis of variance using the Genstat statistical package, version

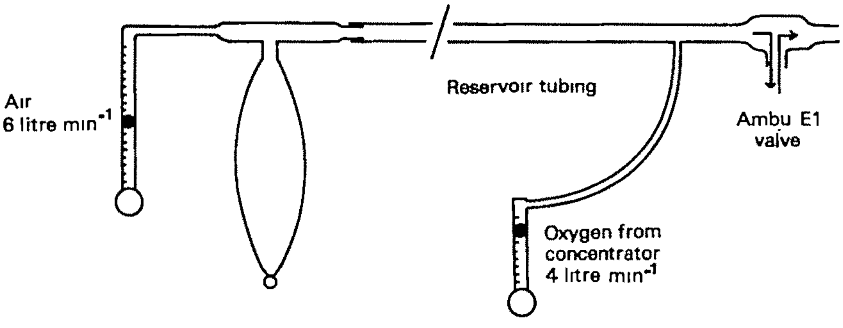

FIG. 1. Circuit for standard drawover technique.

TABLE I. *Mean blood-gas tensions (kPa) for each treatment*

Variable	Air baseline	Magill system	Drawover standard	Drawover reservoir	SE of diff. between treatments	95% CI of each mean
Log Pa_{O_2}	1.136	1.825	1.550	1.864	0.0065	±0.0146
Corresponding Pa_{O_2}	13.7	66.8	35.5	73.1		±3.4%
Pa_{CO_2}	4.82	4.68	4.65	4.74	0.092	±0.29

4.04B (Numerical Algorithms Group Ltd), on a Honeywell mainframe computer running under Multics release 11.0. As the basic "experimental unit" was the subject, the mean of the three values for each treatment in each subject was calculated and the analysis performed on the resulting eight means (four techniques in each of two subjects). This was done for both the Pa_{O_2} and the Pa_{CO_2} data. Analysis was made directly on the Pa_{CO_2} values, but on the logarithms of the Pa_{O_2} data, in order to make the residuals independent of the fitted values. The means for each treatment are shown in table I for log Pa_{O_2} and the corresponding values of Pa_{O_2}, and for Pa_{CO_2}, together with the standard errors of the differences.

RESULTS

The time taken to empty the 20-litre reservoir bag ranged from 2 to 2.5 min, equivalent to a minute volume of 8–10 litre min^{-1}.

The differences between treatments in terms of log Pa_{O_2} were all highly significant: even the small difference between Magill and Drawover–reservoir was six times the SE of the differences between means (table I). The 95% confidence limits for each treatment were ±3.4% of the estimated value (table I). The mean values of Pa_{CO_2} were similar for all treatments: even the largest difference (between baseline and drawover-standard) was only 1.8 times the SE of the differences (table I).

TABLE II. *Performance of Devilbiss Mini VO2*

Concentrator flow (litre min^{-1})	Oxygen (%)
2	95
3	91
4	82
5	72

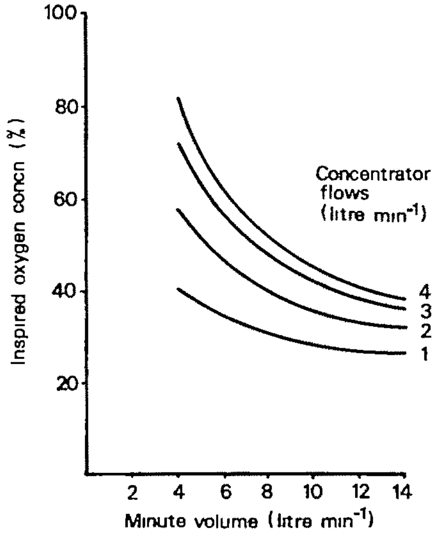

FIG. 2. Predicted inspired oxygen concentrations.

The output of the concentrator used in the study is shown in table II. Figure 2 allows the inspired oxygen concentrations from a drawover anaesthetic system to be determined for different ventilation rates and concentrator flow settings.

DISCUSSION

Preoxygenation increases the safety of anaesthesia, particularly around the time of tracheal intubation and extubation, by increasing pulmonary oxygen stores. The immediate administration of a high concentration of oxygen may be lifesaving when severe hypoxia occurs such as during cardiac arrest. Although oxygen concentrators of the domestic type are revolutionizing oxygen supply in rural hospitals in developing countries, they are limited by inability to produce a high flow of oxygen. Our results show that the standard technique used for preoxygenation with an oxygen concentrator and a standard drawover anaesthetic circuit is relatively ineffective compared with a method using a prefilled reservoir bag [9]. When the standard drawover technique of preoxygenation is in use, the $F_{I_{O_2}}$ which is inspired may be read from figure 2. In our experiment we chose to examine a minute ventilation ($\dot{V}$) of 10 litre min^{-1} so as to simulate the mild hyperventilation of preoxygenation, a common occurrence, particularly with obstetric patients. At this $\dot{V}$, the $F_{I_{O_2}}$ was about 45% and the resulting Pa_{O_2} (and therefore denitrogenation) 50% of that achieved by the other methods. More pronounced hyperventilation would have reduced $F_{I_{O_2}}$ further, making denitrogenation even less effective.

The technique of preoxygenation using a 20-litre reservoir was as effective as the Magill technique with 100% oxygen. The reservoir bag was constructed from materials which would be available in any part of the world: in our case we used a plastic disposable bin liner. The size was reduced to 20 litre (measured by the time to fill with a Boyle's machine rotameter set at 5 litre min^{-1}) by the application of tape around the neck of the bag, which was attached to a standard connector. Previously a 40-litre reservoir has been recommended [9], but our results indicate that a 20-litre reservoir is an effective volume for preoxygenation. When used in anaesthesia, this bag should be filled from the concentrator running at 2 litre min^{-1} and left ready for emergency use. In urgent situations a higher rate of filling from the concentrator would be effective. It would provide an immediate supply of 95% oxygen for preoxygenation, emergency administration of oxygen, or even during neonatal resuscitation, when it could be connected to a paediatric self-inflating bag. Previous studies [2–4] have shown that oxygen concentrators take 5–10 min to reach their full oxygen output. It is likely that the use of a prefilled reservoir would facilitate induction in emergency patients.

We note that the Triservice apparatus (Penlon U.K. Ltd) is supplied with the Houtonox oxygen valve, which is an oxygen pressure reducing valve providing a choice of oxygen flows of 1 or 4 litre min^{-1}, with the recommendation that the greater flow is used for preoxygenation [10]. For preoxygenation, a flow of 4 litre min^{-1} is likely to be inadequate for full denitrogenation and the 20-litre reservoir is likely to be of benefit [9].

When an oxygen concentrator is used as an oxygen source for anaesthesia or for a ventilator, the graph shown in figure 2 may be used to predict the $F_{I_{O_2}}$ by relating the concentrator "oxygen" flow and the total ventilation. The value could be checked if an oxygen analyser was available. Although our results refer specifically to the Devilbiss concentrator studied, we feel that they may be applied to the majority of domiciliary concentrators, as most models in this flow range perform to a similar specification [2–4].

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EFFECT OF DIFFERENT RATES OF INFUSION OF PROPOFOL FOR INDUCTION OF ANAESTHESIA IN ELDERLY PATIENTS

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SUMMARY

The effect of changing the rate of infusion of propofol for induction of anaesthesia was studied in 60 elderly patients. Propofol was administered at 300, 600 or 1200 ml h^{-1} until loss of consciousness (as judged by loss of verbal contact with the patient) had been achieved. The duration of induction was significantly longer ($P < 0.001$) with the slower infusion rates (104, 68 and 51 s), but the total dose used was significantly less ($P < 0.001$) in these patients (1.2, 1.6 and 2.5 mg kg^{-1}, respectively). The decrease in systolic and diastolic arterial pressure was significantly less in the 300-ml h^{-1} group at the end of induction and immediately after induction ($P < 0.01$). The incidence of apnoea was also significantly less in the slower infusion group.

KEY WORDS

Anaesthetic techniques: infusions. Anaesthetics, intravenous: propofol.

Induction of anaesthesia with propofol commonly produces a decrease in arterial pressure and transient apnoea. The reported decrease in arterial pressure varies between 15 and 40% and is greater than that seen with other induction agents [1–3]. It is increased by concomitant administration of other agents (including premedicants) and is dose- and age-related [1, 4, 5]. The cause of the hypotension is uncertain; a reduction in cardiac output [6] or systemic vascular resistance [7] has been suggested, although the most likely cause is a reduction in both [8–10]. Decreases in arterial pressure are particularly undesirable in the elderly and high risk groups, so that the advantage of rapid recovery and the absence of effect on heart rate and pulmonary arterial pressure [11] may be negated [12].

In the present study we have examined the effects of different rates of infusion of propofol on arterial pressure and heart rate during induction of anaesthesia in elderly patients, using a new syringe pump with infusion rates of 300, 600 and 1200 ml h^{-1} (5, 10 and 20 ml min^{-1}). The Ohmeda 9000 pump also delivers infusion rates of 0.1–200 ml h^{-1} when not used in the "rapid infusion" mode. The pump is lightweight and versatile and permits a rapid transition between fast and slow rates of infusion.

PATIENTS AND METHODS

We studied 60 patients (ASA I, II or III aged 60 yr or older) undergoing body surface or urological surgery lasting 30–60 min and not requiring tracheal intubation as part of the anaesthetic technique. Patients were excluded if they had clinical evidence of severe respiratory, cardiovascular, hepatic, renal or endocrine disease, uncontrolled hypertension, previous adverse response to general anaesthesia, if their body weight was more than 20% greater than ideal or they were taking any drug likely to influence the course of anaesthesia or haemodynamic response.

The study was approved by the local Ethics

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Committee and all patients gave written informed consent. Temazepam 20 mg was given orally 1 h before induction of anaesthesia. In the anaesthetic room an arm vein was cannulated and non-invasive monitoring of arterial pressure commenced using the contralateral arm.

All patients were given fentanyl 0.75 $\mu g\ kg^{-1}$ i.v. 5 min before induction of anaesthesia. They were allocated randomly to one of three groups to receive propofol at 300, 600 or 1200 $ml\ h^{-1}$ for induction of anaesthesia. Anaesthesia was defined as loss of verbal contact with the patient; at this point, the rapid infusion was stopped. The patients breathed 66% nitrous oxide in oxygen spontaneously via a mask and a Mapleson D system. An infusion of propofol at a rate equivalent to 6 $mg\ kg^{-1}\ h^{-1}$ was used to maintain anaesthesia. This infusion was altered according to clinical requirements as judged by patient movement or cardiovascular responses and any alterations were recorded. The infusion of propofol was discontinued just before the end of surgery, but the nitrous oxide was maintained until surgery was completed.

Arterial pressure and heart rate were measured using a Dinamap monitor. Cardiovascular measurements were made before and 4 min after administration of fentanyl, at the end of induction, at 2 and 5 min after induction and at 5-min intervals thereafter during maintenance of anaesthesia.

At the end of induction, a venous blood sample was obtained from the arm contralateral to that receiving the infusion of propofol, for assay of plasma concentration of propofol. Other measurements recorded at this time were duration of induction, induction dose and rate of infusion. Duration of induction was taken as the time from commencement of infusion to loss of verbal contact. The induction dose was the amount of drug delivered in this period and the rate was recorded from the syringe driver.

Any period of apnoea (> 30 s) after induction was recorded, together with any excitatory effects.

At the end of surgery, recovery times to spontaneous eye opening and time to full orientation as judged by the ability to give their correct date of birth were recorded. The patients were asked also if induction of anaesthesia was pleasant or unpleasant and questioned for recall of other events. The presence of excitatory or other side effects was recorded during recovery.

Statistical analysis was performed using the Kruskal–Wallis test for induction times, induction doses and plasma concentrations of propofol. Repeat measures analysis of variance was used to compare percentage changes from baseline for arterial pressures and heart rate at sequential time points. Where statistical significance was found between the three groups (taken as $P < 0.05$), pairs of results were compared using two-tailed Wilcoxon rank sum test. Fisher's exact test was used to compare other data.

RESULTS

There was no significant difference between the groups for age, sex, weight, height or ASA status (table I). All patients were anaesthetized successfully using the regimen described.

Induction times were significantly longer with the slower infusion rates (mean 104, 68 and 51 s, at rates of 300, 600 and 1200 $ml\ h^{-1}$, respectively) ($P < 0.001$ for each of the three possible comparisons). There was also a significant difference ($P < 0.001$) between induction doses in the three

TABLE I. *Demographic data of patients, induction times and doses (mean (SD)).* *$P < 0.001$ *between groups (Kruskal–Wallis)*

	Infusion rate ($ml\ h^{-1}$)		
	300	600	1200
Age (yr)	71.7 (6.5)	72.9 (6.8)	72.7 (6.3)
Sex (M:F)	17:3	18:2	17:3
Weight (kg)	70.7 (9.0)	70.0 (7.4)	68.0 (11.5)
Height (cm)	170.9 (9.4)	168.9 (8.5)	172.8 (8.6)
ASA (I, II, III)	7, 11, 2	6, 13, 1	6, 11, 3
Duration of surgery (min)	48.1 (13.0)	41.9 (10.2)	53.8 (25.2)
Induction time (s)*	103.5 (25.2)	67.6 (11.7)	51.1 (8.5)
Dose (mg)*	87.1 (16.9)	111.8 (18.6)	167.8 (25.2)
Dose ($mg\ kg^{-1}$)*	1.24 (0.25)	1.60 (0.25)	2.52 (0.48)

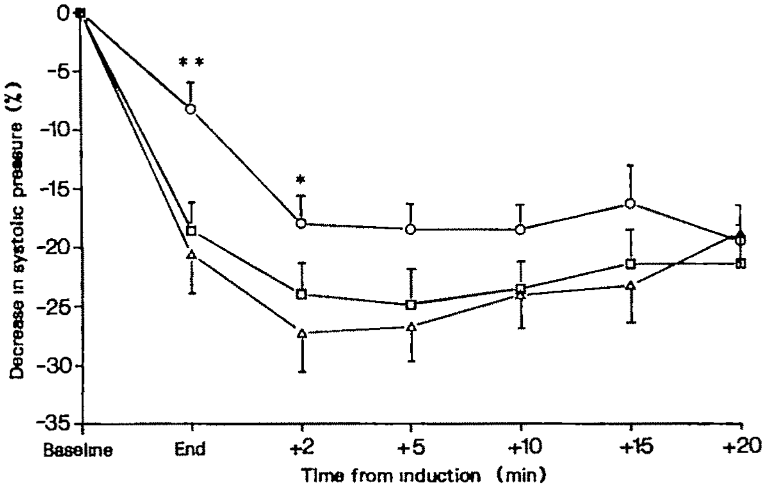

FIG. 1. Percentage decrease in systolic pressure (mean, SEM) with time after induction of anaesthesia with propofol 300 ml h^{-1} (○), 600 ml h^{-1} (□) and 1200 ml hr^{-1} (△). *$P < 0.05$; **$P < 0.01$.

TABLE II. *Systolic (SAP) and diastolic (DAP) arterial pressures and heart rate (mean (SD)).* *$P < 0.05$; **$P < 0.01$ *(repeat measures ANOVA between groups compared with baseline)*

	Infusion rate (ml h^{-1})		
Time (min)	300	600	1200
SAP (mm Hg)			
Baseline	152.5 (16.7)	150.9 (24.1)	141.8 (11.7)
End induction**	139.0 (17.1)	121.2 (17.9)	112.9 (19.9)
+2*	123.6 (18.7)	113.2 (20.1)	103.4 (19.5)
+5	123.7 (18.9)	112.2 (24.1)	103.6 (15.5)
+10	122.8 (13.5)	113.2 (18.1)	107.6 (14.7)
+15	125.8 (17.9)	116.6 (19.4)	108.3 (14.8)
+20	121.2 (18.5)	116.2 (19.3)	113.8 (14.2)
+25	121.9 (16.2)	119.1 (20.8)	112.3 (13.8)
+30	124.2 (17.6)	118.2 (23.2)	112.1 (13.5)
DAP (mm Hg)			
Baseline	86.3 (13.3)	82.5 (20.9)	87.5 (12.1)
End induction*	77.3 (14.1)	67.8 (17.5)	66.6 (13.6)
+2	72.4 (12.9)	64.9 (18.5)	65.1 (11.8)
+5*	70.2 (12.4)	64.9 (19.1)	61.9 (10.4)
+10	68.3 (8.8)	64.4 (16.8)	61.7 (9.7)
+15	72.8 (15.5)	64.0 (17.5)	65.2 (11.0)
+20	68.8 (13.1)	65.7 (17.8)	66.9 (11.4)
+25	70.7 (11.9)	70.6 (14.0)	67.1 (11.1)
+30	70.5 (12.7)	68.7 (12.2)	68.3 (12.7)
Heart rate (beat min^{-1})			
Baseline	68.9 (12.0)	68.9 (13.4)	76.9 (13.2)
End induction	72.6 (11.7)	69.6 (9.8)	74.5 (11.5)
+2	66.2 (12.1)	67.7 (8.9)	75.3 (10.7)
+5	65.7 (10.9)	63.7 (8.9)	71.3 (8.6)
+10	64.0 (9.9)	60.3 (9.5)	68.8 (8.6)
+15	64.5 (10.9)	59.2 (9.2)	68.1 (9.9)
+20	64.0 (10.5)	60.0 (8.2)	68.3 (9.0)
+25	64.8 (10.2)	60.2 (8.2)	67.7 (8.9)
+30	63.1 (10.1)	61.9 (9.1)	69.1 (10.1)

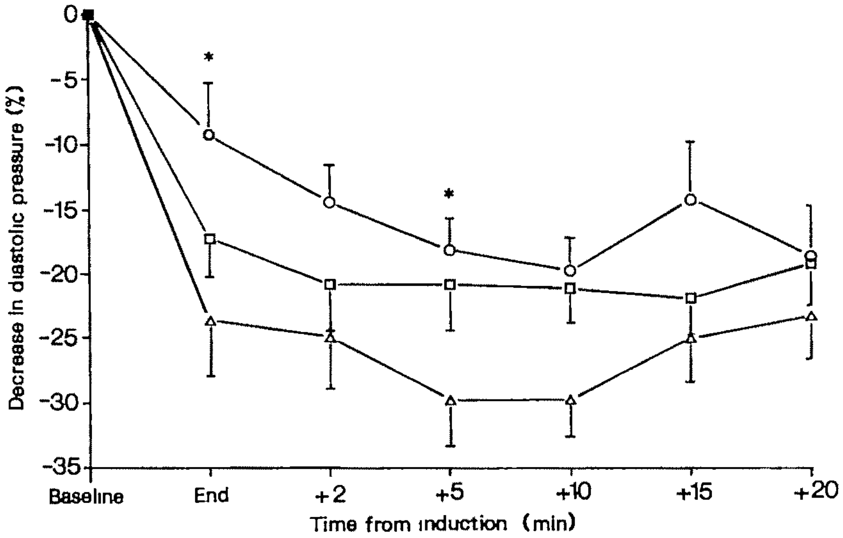

FIG. 2. Percentage decrease in diastolic pressure (mean, SEM) with time after induction of anaesthesia with propofol 300 ml h^{-1} (○), 600 ml h^{-1} (□) and 1200 ml h^{-1} (△). * $P < 0.05$.

groups (table I). The mean total and weight-related induction dose was significantly less at the slower infusion rates ($P < 0.001$ for each of the three possible comparisons) (mean 1.2, 1.6 and 2.5 mg kg^{-1}, respectively).

There were significant differences in the percentage changes in systolic arterial pressures from baseline (fig. 1, table II) at the end of induction ($P < 0.01$) and at +2 min ($P < 0.05$) between the 300-ml h^{-1} group and the other two groups (at end of induction: $P < 0.001$ for 300 *vs* 600 and 1200 ml h^{-1}; at +2 min: $P < 0.01$ for 300 *vs* 600 and 1200 ml h^{-1}).

The differences in diastolic arterial pressure (fig. 2, table II) were significant between the three groups at the end of induction and at +5 min ($P < 0.05$ for 300 *vs* 600 ml h^{-1} and for 600 *vs* 1200 ml h^{-1}; $P < 0.01$ for 300 *vs* 1200 ml h^{-1} at both times). No other significant differences were noted.

There were no significant changes in heart rate (table II) between the three groups or between different times.

There were no significant differences in the blood concentrations of propofol (mean 4.7, 6.1 and 9.5 μg ml^{-1}) between the groups at the end of induction (fig. 3). Maintenance doses did not differ between the three groups at any time (table III).

There was a significant difference in the incidence of apnoea between the three groups ($P < 0.01$). Eight patients had apnoea in the 1200-ml h^{-1} group, compared with three in the 600-ml h^{-1} group and none in the 300-ml h^{-1} group. There were no significant differences between groups for incidence of other side effects. Four patients suffered pain on injection (two in

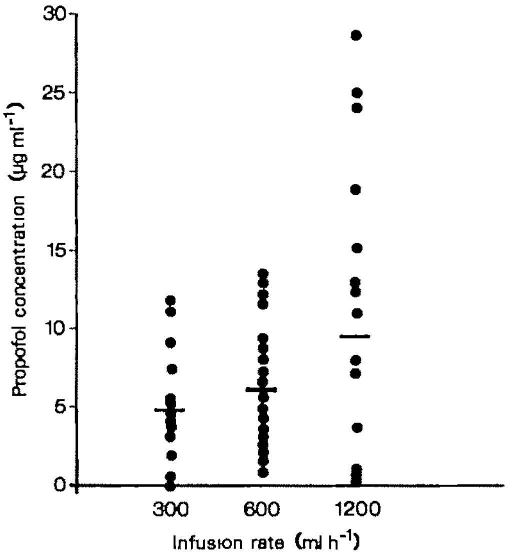

FIG. 3. Plasma concentrations of propofol at end of induction. No significant differences between groups. — = Mean concentration.

TABLE III. *Plasma concentrations of propofol at end of induction (mean and range) and maintenance doses (mean (SD)). No significant differences in concentrations or maintenance doses between groups. Mean maintenance rate defined as total dose/duration*

	Induction rate (ml h^{-1})		
	300	600	1200
Propofol concentration (μg ml^{-1})	4.7 (0.44–11.7)	6.1 (0.79–13.3)	9.5 (0.56–28.50)
Maintenance doses (mg kg^{-1})			
0–10 min	1.16 (0.33)	1.00 (0.27)	0.99 (0.33)
11–20 min	1.11 (0.39)	0.96 (0.20)	1.18 (0.39)
21–30 min	1.08 (0.26)	1.00 (0.22)	1.00 (0.27)
Mean maintenance rate (mg kg^{-1} h^{-1})	6.40 (1.64)	5.57 (1.01)	6.02 (1.60)

the 600-ml h^{-1} and two in the 1200-ml h^{-1} groups); one patient had hiccups (1200-ml h^{-1} group).

There were no differences in recovery times from end of surgery between the groups as measured by time to open eyes (mean times 9.3, 8.3 and 9.9 min, respectively, for the 300-, 600- and 1200-ml h^{-1} groups) or give correct date of birth (mean times 12.4, 10.3 and 13.6 min, respectively).

DISCUSSION

Previous studies [13, 14] have examined the reduction in arterial pressure with different rates of injection of propofol for induction of anaesthesia. All these studies used fixed doses of agent based on weight and given over 5–80 s. They showed that the rate of injection altered the time for induction of anaesthesia, but did not show a difference in haemodynamic response. We are unaware of any study in which the induction agent was administered at variable rate to a fixed end-point such as loss of consciousness, although Dundee and colleagues [5] reported a lesser incidence of severe hypotension when a dose of 1.25 mg kg^{-1} was followed by 10-mg incremental doses at 15-s intervals until loss of consciousness was obtained. We proposed that a slower infusion of propofol to a fixed end-point rather than a fixed dose would result in lesser changes in arterial pressure.

Our results confirm those of Rolly [13] and Gillies [14], both of whom showed an increased induction time with slower speeds of injection. However, in our study the slower infusion rates, despite increased induction times, resulted in lesser induction doses of propofol with no significant differences in the plasma concentrations of propofol at the end of induction. The mean induction dose of 1.24 mg kg^{-1} given at 300 ml h^{-1} is considerably less than the standard dose of 2–2.5 mg kg^{-1} [15], although the resultant concentration of propofol was similar to that reported for the greater dose in healthy patients [16]. Other workers have quoted adequate induction doses in the elderly of 1.4–1.5 mg kg^{-1} [17, 18] after premedication and 1.5–1.75 mg kg^{-1} in unpremedicated patients [4, 5]. Although there were no significant differences in the plasma concentrations of propofol at the end of induction, the mean concentration was greater in the faster infusion groups than the slower group. This is likely to be caused by the greater doses administered at the faster rates and not by the previously described differences in the pharmacokinetics of propofol in the elderly [16, 19].

The slower infusion rates also produced less decrease in arterial pressure at the end of induction and immediately after, compared with the faster infusion rates. The mean percentage decrease in arterial pressure after the 300-ml h^{-1} infusion rate was 8.3% at the end of induction and 18.1% 2 min after induction, compared with decreases of 20% in younger patients [8], 18.6% in children [20] and as much as 30% in elderly patients [17]. The reduction after the 600- and 1200-ml h^{-1} infusions was similar to that found by Claeys [6].

Apnoea occurred less often with the 300-ml h^{-1} induction rate compared with the faster rates. Previous studies have reported the incidence of apnoea as 78–100% [9, 21] in elderly patients

[9], and 20–30% [22, 23] in younger patients when apnoea is defined as a ventilatory pause of greater than 30 s or 40 s, respectively. The overall incidence of apnoea of 6.6% in the current study is much less, despite prior administration of fentanyl.

The other side effect seen less commonly (compared with previous studies) was the presence of pain during injection. Only four (6.6%) patients complained of pain during administration of the induction dose, although the subjects were not questioned closely to determine the incidence of mild discomfort. The majority of patients (48 of 60) had the i.v. cannula inserted at the wrist or on the dorsum of the hand, which commonly results in an incidence of pain during injection of about 30% [2, 24]. The only difference compared with previously reported work that may explain the lesser incidence of apnoea and pain is the slow rate of infusion of propofol for induction of anaesthesia, in this case through a slow running i.v. infusion.

The differences in observed effects at the greater infusion rates are probably a reflection of the greater doses administered at these rates, even though the drug was titrated to the same end-point in all patients. It is postulated that this effect is produced by accumulation of drug within the venous system because of the slow circulation time in elderly patients and hence a delay between administration of the drug and observed effect. This would also explain the greater mean plasma concentrations of propofol observed with the faster infusion rates.

Two potential problems of the slower rates of induction would be that the patients might find the duration of induction unpleasant, or the quality of anaesthesia would be inferior. All patients were blind to the rate of infusion and reported induction to be smooth and pleasant. The anaesthetists were not blind to the infusion rate, but reported only two patients in whom prolonged apnoea or marked hypotension occurred. Both patients were in the 1200-ml h^{-1} group. There were no postoperative sequelae in either of these or any other patients.

The syringe driver used to induce anaesthesia produced clinically acceptable results for the anaesthetist and the patient. The slower administration of propofol for the induction of anaesthesia in elderly patients reduced the incidence of unwanted side effects and the total dose required.

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CARDIOVASCULAR EFFECTS OF PROPOFOL AND OF THIOPENTONE ANAESTHESIA IN THE SHEEP

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SUMMARY

We have examined the effects on the cardiovascular system and on regional blood flow of propofol and thiopentone when administered with IPPV (F_{IO_2} 0.4). A longitudinal study design was used in which 16 studies were performed in eight sheep for 30 min before, during the last 30 min of 70 min anaesthesia, and for 6 h after anaesthesia. During anaesthesia with propofol and thiopentone, mean total body oxygen consumption decreased, respectively, by 47% ($P < 0.001$) and 24% ($P < 0.01$) of pre-anaesthesia baseline values, mean heart rate increased by approximately 50% ($P < 0.05$) with both agents, mean arterial pressures increased by approximately 50% ($P < 0.05$) with both agents and the mean cardiac output was unaltered with propofol anaesthesia but was decreased by 20% ($P < 0.05$) with thiopentone anaesthesia. The changes in arterial pressure and heart rate were unexpected and may have been a result of a species-specific effect. Mean hepatic blood flow decreased consistently by a mean of 17% ($P < 0.01$) during propofol anaesthesia, and inconsistently during thiopentone anaesthesia so that it was not significantly different from baseline values. Mean renal blood flow decreased during propofol anaesthesia by 7% ($P < 0.05$) and by 27% ($P < 0.001$) during thiopentone anaesthesia. Whereas most variables returned to baseline values within 2 h after propofol anaesthesia, this took 5 h after thiopentone anaesthesia.

KEY WORDS

Anaesthetics, intravenous: propofol, thiopentone. Heart: mean arterial pressure, heart rate, cardiac output. Liver: hepatic blood flow. Kidney: renal blood flow.

The use of propofol for induction and maintenance of anaesthesia by repeated doses or infusion has become widespread in recent anaesthetic practice [1]. There has also been a resurgence of interest in the continuous use of thiopentone for anaesthesia [2]. In most situations, the cardiovascular effects of these agents have been studied in surgical patients in whom the effects of premedicants, surgical stimulus or inhalation anaesthetic agents may have contributed to the observed effects. Also, to date, studies of the effects of propofol on regional blood flow have not been reported. We have studied, therefore, the cardiovascular effects of these agents, in the absence of surgery and other pharmacological agents, using a sheep preparation in which the effects during and after anaesthesia could be compared with baseline measurements in the same animals before anaesthesia.

METHODS

Animal preparation

Sixteen studies were performed in eight sheep prepared previously with chronically implanted catheters so that the cardiovascular effects of total i.v. anaesthesia with thiopentone and of propofol could be measured. At the same time, the regional clearances of several indicators and drugs were

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measured. The details of these studies are presented in accompanying papers. The surgery, the physiological profile of the sheep preparation, and some applications in anaesthesia research have been reported previously in detail [3–5]; the aspects relevant to this study are described briefly here.

Adult merino ewes (weight 33–63 kg) were prepared by placement, under general anaesthesia, of polyethylene catheters so that their tips were at the aortic arch for the measurement of mean arterial pressure and the sampling of arterial blood, in the right atrium for the infusion of drugs, indicator substances and i.v. crystalloid solutions, and in a right hepatic vein, the left renal vein and the posterior vena cava (distal to the site of entry of the renal veins) for sampling, respectively, of hepatic, renal and hindquarter effluent blood. In addition, a quadruple-lumen thermistor-tipped catheter was placed in a pulmonary artery for the measurement of cardiac output. At least 1 week was allowed between catheter placement and study.

Experimental design

The studies were divided into two parts, one using the antibiotic drug cefoxitin as an indicator to examine the efficacy of renal elimination of drug [6] and the other using the analgesic agent, pethidine, as indicators to examine the efficacy of hepatic and other routes of elimination of drug [7]. In both parts, renal blood flow was determined using sodium hippuran and hepatic blood flow was determined using sodium bromsulphthalein (BSP) as indicator substances. The infusions of the indicators and drugs were continued throughout the entire study period; the doses used have been shown not to produce significant cardiovascular effects [6, 7].

The first 60-min period was designated as a rest period to allow the animal to adapt to the study room and for the substances to achieve stable blood concentrations. During the next 30-min period, observations were made and appropriate blood samples were collected 10 min apart (i.e. four sets) for baseline measurements. Anaesthesia was induced with commercial preparations of either propofol 250–300 mg over 1 min or thiopentone 750 mg over 1 min, a cuffed tracheal tube was inserted into the trachea and the lungs ventilated to normocapnia with an $F\text{I}_{\text{O}_2}$ of 0.4. Maintenance infusions of propofol 20–25 mg min^{-1} at a constant rate or thiopentone 25 mg min^{-1} decreasing to 10 mg min^{-1} over the first 30 min were continued for 70 min; the last 30 min of this period was observed as the "anaesthesia" period and measurements were made as for the baseline period. The doses were determined from experience in our laboratory of producing anaesthesia in sheep with these agents. Recovery was observed by repeating the measurements at 0.5, 1.0, 2, 3, 4, 5, 6, 7, 8 and 9 h after the maintenance infusions were stopped. For statistical analysis, these measurements were grouped into early (0.5–2 h), mid (3–5 h) and late (6–9 h) recovery periods.

Arterial blood concentrations of propofol [8] and thiopentone (see Appendix 1) each were measured by high pressure liquid chromatography (HPLC) to relate the results to published anaesthetic blood drug concentrations. The sensitivity of both assays was 0.02 mg litre^{-1}. The coefficients of variation of the assays for propofol and thiopentone, determined at concentrations of 2.0 mg litre^{-1} were, respectively, 3.6% and 2.4%.

Cardiovascular measurements

A saline-filled extension line was connected to an aortic catheter and to a calibrated anaeroid gauge to measure mean arterial pressure. Heart rate was determined by counting the rate of oscillation of a small air bubble placed in this line. Cardiac output was determined by thermodilution with a commercially available cardiac output computer after right atrial injection of ice-cold saline and corrected in each animal by calibration against dye dilution. Standard Fick methods were used for measurement of hepatic and renal blood flows. Hepatic blood flows were determined from the ratios of infusion rates to arterio–hepatic venous blood concentration differences of BSP (3.8 mg min^{-1} infused into the right atrium and measured by HPLC [3]). The sensitivity of the assay was 0.2 mg litre^{-1} and the coefficients of variation of the assay at concentrations of 3.0 and 1.0 mg litre^{-1} (typical arterial and hepatic venous concentrations) were 2.8 and 2.0%, respectively. Renal blood flows were determined from the ratios of infusion rates to aortic–renal venous blood concentration differences of hippuran sodium (15 mg min^{-1} infused into the right atrium and analysed by HPLC, see Appendix 2). The sensitivity of the assay was 0.2 mg litre^{-1} and the coefficients of variation of the assay at 25 and 2 mg litre^{-1} (typical arterial and renal venous concentrations) were 1.0 and 1.3%, respectively.

TABLE I. *Baseline values in adult merino ewes during constant rate infusions of pethidine or cefoxitin, bromsulphthalein (BSP) and hippuran. Means* (SD) *of eight animals except* *n = 7 *or* †n = 6

	Anaesthetic	
	Propofol	Thiopentone
Heart rate (beat min^{-1})	92 (23)	89 (19)
Mean arterial pressure (mm Hg)	76 (15)	83 (12)
Cardiac output (litre min^{-1})	6.3 (1.1)	5.7 (0.9)*
Hepatic blood flow (litre min^{-1})	1.50 (0.50)	1.45 (0.24)
Renal blood flow (litre min^{-1})	0.72 (0.06)†	0.97 (0.28)*

Total body oxygen consumption

The total body oxygen consumption was measured in 13 of these studies, to relate the results of this study to others in this laboratory. It was determined from the product of cardiac output and the arterial–pulmonary arterial oxygen content difference. Blood oxygen content was measured using a commercially available Lex-O_2-Con apparatus (Lexington Instrument Corp., Waltham, Massachusetts, U.S.A.).

Statistical analysis

A longitudinal study design was used that permitted detection of significance with small sample sizes. On inspection, the absence of obvious cardiovascular effects and differences between the studies using cefoxitin and pethidine was confirmed [5]. Hence, the results from these studies were pooled. The baseline values of each variable in each individual study have been tabulated in absolute units (table I). The respective mean value in the "baseline" period of each individual study was assigned a value of 100% and one-sample *t* tests against this value were performed for each parameter expressed as percentage means and SD of the corresponding baseline values. Two-tailed probabilities of $P < 0.05$ were considered statistically significant.

RESULTS

The values of mean arterial pressure, heart rate, cardiac output and renal and hepatic blood flows before anaesthesia (baseline values) are given in table I; those during and after anaesthesia have been shown in figures 1 and 2 as the percentage means and SD of the individual mean baseline values in the same study. The overall mean arterial blood concentration of propofol during anaesthesia was 6.8 (SD 2.6) mg $litre^{-1}$; that of thiopentone was 47 (21) mg $litre^{-1}$. Individual mean values of arterial blood propofol concentrations during anaesthesia for the animals receiving pethidine were 4.9 (1.7), 7.9 (1.1), 9.2 (2.2) and 7.9 (0.7) mg $litre^{-1}$; those for the animals receiving cefoxitin were 3.0 (1.3), 8.7 (3.5), 7.6 (1.4) and 8.0

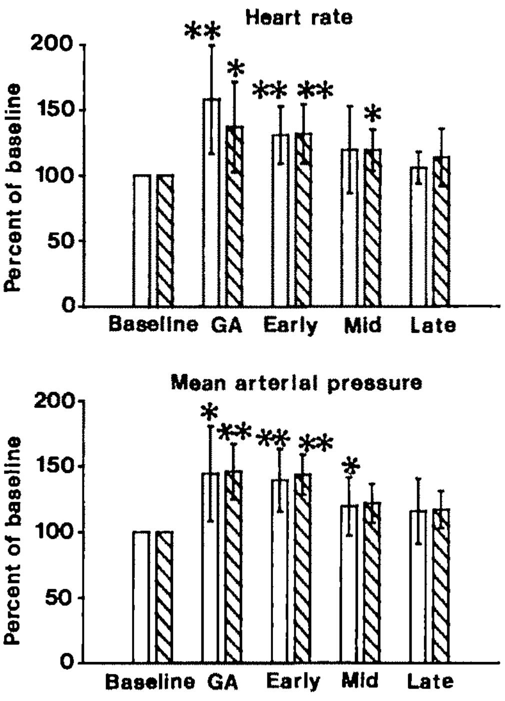

FIG. 1. Effects of propofol (open panels) or thiopentone (hatched panels) anaesthesia on heart rate and mean arterial pressure in the sheep. To facilitate comparisons in this and accompanying figures, the mean values during a 30-min baseline period have been assigned a value of 100% and values during subsequent test periods have been expressed as mean (SD) of the mean baseline values in the respective studies. Test periods were observed during the last 30-min of a 70-min period of anaesthesia (GA), during early recovery after anaesthesia (0.5–2 h), during mid recovery after anaesthesia (3–5 h) and during late recovery after anaesthesia (6–9 h). Significant differences compared with baseline (two-tailed): $*P < 0.05$; $**P < 0.01$.

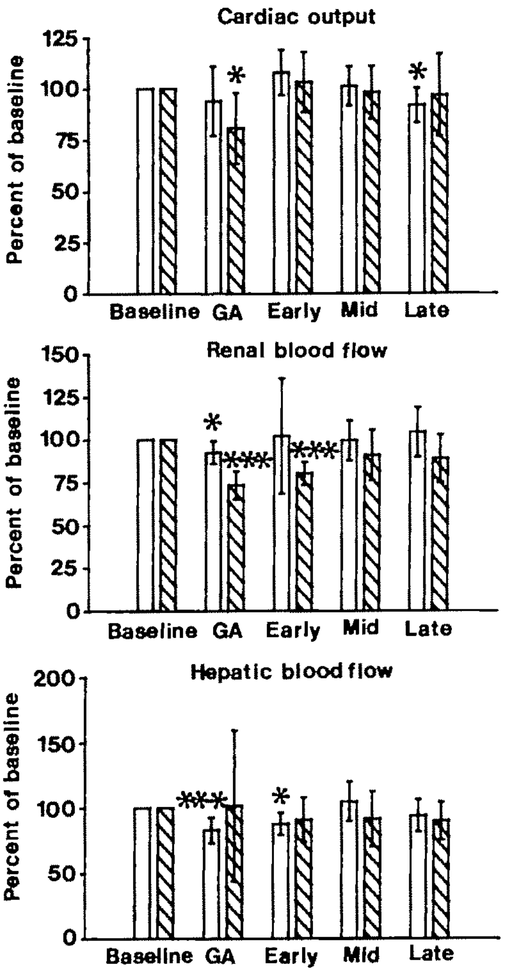

FIG. 2. Effects of propofol (open panels) or thiopentone (hatched panels) anaesthesia on cardiac output, renal blood flow and hepatic blood flow in the sheep. To facilitate comparisons in this and accompanying figures, the mean values during a 30-min baseline period have been assigned a value of 100% and values during subsequent test periods have been expressed as mean (SD) of the mean baseline values in the respective studies. Test periods were observed during the last 30 min of a 70-min period of anaesthesia (GA), during early recovery after anaesthesia (0.5–2 h), during mid recovery after anaesthesia (3–5 h) and during late recovery after anaesthesia (6–9 h). Significant differences compared with baseline (two-tailed): $*P < 0.05$; $***P < 0.001$.

(0.8) mg litre^{-1}. Individual mean values of arterial blood concentrations of thiopentone during anaesthesia in the animals receiving pethidine were respectively, not obtained for the first two animals, 32.7 (1.6) and 46.5 (0.6) mg litre^{-1}; those for the animals receiving cefoxitin were, respectively, 25.0 (2.0), 41.0 (4.4), 75.3 (12.1) and 45.7 (6.0) mg litre^{-1}.

The mean heart rate (fig. 1) during anaesthesia with propofol was 158 (41)% of baseline ($P < 0.01$) and that during anaesthesia with thiopentone was 137 (35)% of baseline ($P < 0.05$). Recovery to baseline values occurred during the late recovery period after both propofol and thiopentone anaesthesia. The mean of the mean arterial pressures (fig. 1) increased during propofol anaesthesia to 144 (36)% of baseline ($P < 0.05$) and to 146 (21)% of baseline ($P < 0.001$) during thiopentone anaesthesia. Recovery to baseline values occurred during the late recovery period after both propofol and thiopentone anaesthesia.

Mean cardiac output was 94 (17)% of baseline (ns) during propofol anaesthesia and 81 (17)% of baseline ($P < 0.05$, $n = 6$) during thiopentone anaesthesia (fig. 2). Mean renal blood flow decreased during propofol anaesthesia to 93 (7)% of baseline ($P < 0.05$, $n = 6$) and to 74 (9)% of baseline ($P < 0.001$, $n = 7$) during thiopentone anaesthesia; the duration of the effect was greater after thiopentone (fig. 2). Mean hepatic blood flow (fig. 2) decreased during propofol anaesthesia to 83 (10)% of baseline ($P < 0.001$, $n = 7$). During thiopentone anaesthesia, five of seven animals had a decreased mean hepatic blood flow, in one animal mean hepatic blood flow was virtually unchanged and in the other animal mean hepatic blood flow increased (to 228% of baseline), so that the overall mean hepatic blood flow was 102 (58)% of baseline (fig. 2).

During propofol anaesthesia, the total body oxygen consumption decreased to 57 (23)% ($P < 0.01$, $n = 7$); during thiopentone anaesthesia, it was decreased to 76 (12)% of baseline ($P < 0.01$, $n = 6$).

DISCUSSION

Despite many reports on thiopentone and propofol, there is little information on their cardiovascular effects when used alone for the maintenance of anaesthesia. In these sheep, anaesthesia with propofol for 70 min produced an increased heart rate and mean arterial pressure, and decreased hepatic and renal blood flows. Anaesthesia with thiopentone produced similar changes in heart rate and mean arterial pressure, and decreases in cardiac output and renal blood flow and in hepatic blood flow in five of seven animals. Although cefoxitin and pethidine also were infused throughout the studies, we have shown previously that these drugs, at the dose rates used in this study, produced no significant cardiovascular changes [5–7].

Thiopentone has become the standard with which all other i.v. anaesthetics are compared [9], but it has been studied principally in relation to induction of anaesthesia, most frequently in premedicated patients. The direct myocardial depressant effects of thiopentone are well-known: a decreased cardiac output usually occurs, associated with a decreased stroke volume and an increased heart rate [9, 10]. Hypotension usually occurs depending, among other factors, on the rate of thiopentone injection and the degree of compensatory increase in total systemic vascular resistance. Recent reports suggest that relatively greater hypotension usually occurs with propofol induction of anaesthesia [11–13].

In these studies, the increased heart rate and mean arterial pressure during the maintenance of anaesthesia with propofol and with thiopentone were unexpected. The mechanism of these changes is not known. In patients, induction and maintenance of anaesthesia with propofol are associated with decreased mean arterial pressure [14]. Thus it is uncertain if the observed effects were species-specific effects of these anaesthetic agents in sheep or were a result of the animals being only lightly anaesthetized and being stimulated by the tracheal tube. While no specific measures of reflex suppression were made, there is evidence against the latter possibility. First, the total body oxygen consumption was reduced significantly to extents similar to those observed for 1–1.5% halothane and 2% isoflurane anaesthesia [Selby and colleagues, unpublished observations]. Second, the measured blood anaesthetic concentrations (propofol overall mean 6.8 (2.6) mg litre^{-1} and thiopentone overall mean 47 (21) mg litre^{-1}) were similar to those thought necessary for surgical anaesthesia in humans: propofol 2–4 mg litre^{-1} [15] and thiopentone 10–42 mg litre^{-1} [16, 17]. Moreover, the magnitude of the cardiovascular changes in individual animals did not correlate significantly with the individual mean arterial blood anaesthetic concentrations. If the changes were caused by light anaesthesia, negative correlations might have been expected. Third, the animals did not cough during intubation and tolerated controlled ventilation without the use of neuromuscular blocking drugs. These results, taken together, suggest either that the cardiovascular effects observed were an unusual response to these agents in sheep or that they represent a normal response to the prolonged infusion of either propofol or thiopentone alone without the balancing effects of surgical stimulation.

Whereas both agents usually reduced hepatic blood flow, propofol was more sparing of cardiac output and renal blood flow than was thiopentone. Overall, the i.v. anaesthesia regimens used in these studies disturbed regional blood flow less than did 1 or 1.5% halothane, 2% enflurane or 2% isoflurane (each approximately 1.6 MAC in the sheep) in other studies in this laboratory [5; Selby and colleagues, unpublished observations]. In broad agreement with these results, others have reported that cardiac output in the anaesthetized greyhound remains unaffected by doses of thiopentone equivalent to those used in these studies, but that hepatic blood flow was decreased [18]. It had been suggested that thiopentone induction of anaesthesia caused decreased glomerular filtration rate and renal blood flow secondary, at least in part, to decreased arterial pressure [19, 20]. More recent data from studies in ASA class I and II patients have failed to confirm a decreased renal blood flow from thiopentone induction of anaesthesia [21]. Indeed, other data obtained from induction doses of thiopentone in dogs have shown a transient increase in renal blood flow in parallel with a transient increase in arterial presure [22]. The present study has shown clearly different effects during the maintenance of anaesthesia with either thiopentone or propofol, as decreases in renal blood flow were observed in the presence of increased mean arterial pressure. It has been reported that "light" general anaesthesia (with ether, oxygen and suxamethonium) did not alter glomerular filtration rate or renal blood flow [23]. It would seem, therefore, that the decreased renal blood flow is more likely to be a direct effect of the anaesthetic agents rather than a non-specific consequence of the state of anaesthesia. While the reductions in renal and hepatic blood flows with continuous propofol and thiopentone anaesthesia in the sheep were not related to concomitant changes in arterial pressure, they were of smaller magnitude and shorter duration than those observed for halothane, enflurane and isoflurane under similar circumstances [Selby and colleagues, unpublished observations].

APPENDIX 1

DETERMINATION OF THIOPENTONE BY HPLC

Internal standard solution (thiamylal sodium 25 µg, 25 µl) and acetonitrile 500 µl were added to plasma 0.2 ml in a stoppered polypropylene tube (1.5 ml, Eppendorf). The solution was vortex mixed for 30 s and centrifuged at 3000 *g* for 5 min. Clear supernatant 50 µl was injected into a high pressure liquid chromatograph equipped with a 15-cm, 5-µm C18 reverse phase column and perfused with mobile phase (50:50 methanol:0.1 % sodium dihydrogen phosphate solution containing 5 % methanol and tetrabutyl ammonium phosphate 0.005 mol litre^{-1}) at a flow rate of 2.0 ml min^{-1}. Detection was by u.v. spectroscopy at 280 nm. Under these conditions, the retention times of thiopentone and thiamylal were, respectively, 5.5 and 6.6 min.

APPENDIX 2

DETERMINATION OF HIPPURAN BY HPLC

Internal standard solution (metacetamol 5.0 µg, 25 µl) and acetonitrile 160 µl were added to plasma 0.1 ml in a stoppered polypropylene tube (1.5 ml, Eppendorf). The solution was vortex mixed for 30 s and centrifuged at 3000 *g* for 5 min. Clear supernatant 15 µl was injected into a high pressure liquid chromatograph equipped with a 15-cm, 5-µm C18 reverse phase column, and perfused with mobile phase (5:95 acetonitrile:water containing tetrabutyl ammononium phosphate 0.005 mol litre^{-1}). Detection was by u.v. spectroscopy at 254 nm. Under these conditions, the retention times of para-aminohippurate and metacetamol were, respectively 4.1 and 7.9 min. Iothalamate, with a retention time of 5.8 min, could be quantitated simultaneously, if present.

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EFFECTS OF PROPOFOL AND OF THIOPENTONE ANAESTHESIA ON THE RENAL CLEARANCE OF CEFOXITIN IN THE SHEEP

D. G. SELBY, L. E. MATHER AND W. B. RUNCIMAN

SUMMARY

We have examined the renal extraction ratios and clearances of cefoxitin in three groups of adult merino ewes. One group ($n = 3$) was studied for 12 h without perturbation; these were designated control studies. The other two groups ($n = 4$ each) were studied before (baseline values), during and after the induction and 70-min maintenance of anaesthesia with propofol or thiopentone. In the control studies, mean renal extraction ratio and clearance for cefoxitin were, respectively, 0.67–0.92 and 0.66–0.91 litre min^{-1} and were consistent throughout the entire study period in individual animals. Comparable values were obtained as baseline values in the anaesthesia groups. Compared with individual baseline values, blood concentrations of cefoxitin doubled during anaesthesia with each agent. At the same time, renal extraction ratio and clearance for cefoxitin each decreased significantly to about 50–60% of their control values. Recovery to control values of arterial blood concentrations and renal extraction ratio of cefoxitin took at least 5 h, but recovery of renal clearance was more rapid. The results indicate that renal elimination of an organic anion such as cefoxitin may be affected by changes in renal blood flow and in renal function produced by propofol and thiopentone; these effects may last for several hours after recovery of renal blood flow.

KEY WORDS

Anaesthetics, intravenous: propofol, thiopentone. Kidney renal blood flow, renal extraction ratio, cefoxitin.

It has been observed that the response of the kidney to anaesthesia and surgery is complex [1, 2]. The effects of anaesthesia, alone, on the renal clearance of drugs and other substances are thus difficult to determine and are in need of clarification. With the current interest in the use of propofol and the resurgence of interest in thiopentone for "infusion" anaesthesia, it was decided to study the effects of total anaesthesia with these agents on the renal elimination of cefoxitin, an antibiotic substance which is essentially eliminated totally from the body by glomerular filtration and renal tubular secretion [3], in sheep prepared in such a way as to allow simultaneous cardiovascular and regional pharmacokinetic measurements.

METHODS

The studies were performed in three groups of sheep prepared previously with chronically implanted intravascular cannulae so that the renal blood flow and renal extraction of cefoxitin could be measured. In the first group, studies were performed in the absence of any perturbations: these were designated control studies. The other two groups were studied before (baseline measurements), during (anaesthesia measurements) and after (recovery measurements) total i.v. anaesthesia with propofol or thiopentone. The details of the preparation of the animals, the methods and the cardiovascular effects of propofol and of thiopentone anaesthesia are reported

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elsewhere [4, 5]; only those aspects relevant to this study are reported here.

Adult merino ewes (weight 33–51 kg) were prepared with polyethylene catheters with their tips in the ascending aorta, in the right atrium and in the left renal vein. On the day of each study, right atrial infusions of cefoxitin and hippuran were made for 12 h for measurement of renal blood flow. In the anaesthesia studies, the first 60-min period was designated for loading infusions and to allow the animal to adapt to the study room. During the next 30-min period, observations were made and appropriate blood samples were collected 10 min apart (i.e. four sets) for baseline measurements. Anaesthesia was induced with either propofol 250–300 mg over 1 min ($n = 4$) or thiopentone 750 mg over 1 min ($n = 4$), a cuffed tracheal tube was inserted and the lungs were ventilated to normocapnia with an $F\mathrm{I}_{\mathrm{O}_2}$ of 0.4. Maintenance infusions of propofol 20–25 mg min^{-1} at a constant rate or thiopentone 25 mg min^{-1} reducing to 10 mg min^{-1} over 30 min were continued for 70 min. The last 30 min of this period was observed as the "anaesthesia period" and measurements were made as for the control period. After the maintenance infusions were stopped, recovery was observed by repeating the measurements at 0.5, 1.0, 2, 3, 4, 5, 6, 7, 8 and 9 h. For subsequent statistical analysis, these were grouped into early (0.5–2 h), mid (3–5 h) and late (6–9 h) recovery periods. Arterial blood concentrations of propofol and thiopentone were measured by high pressure liquid chromatography (HPLC) [5, 6] to correlate the dissipation of renal effects with the distribution and metabolism of the anaesthetic agents.

Cefoxitin sodium was infused using a two-stage regimen to produce constant arterial blood concentrations [3]. Loading doses (22.6 mg min^{-1} for 15 min) were followed immediately by maintenance infusions (11.5 mg min^{-1}) for 12 h. Arterial and renal venous blood concentrations of cefoxitin were determined by HPLC [3]. The renal clearances of cefoxitin were determined from the products of the renal blood flow and respective renal extraction ratios.

A longitudinal study design was used in the anaesthesia groups that permitted detection of significance with small sample sizes. The respective mean value in the control periods of each individual study was assigned a value of 100% and one-sample t tests against this value were performed on the means and SD for each parameter

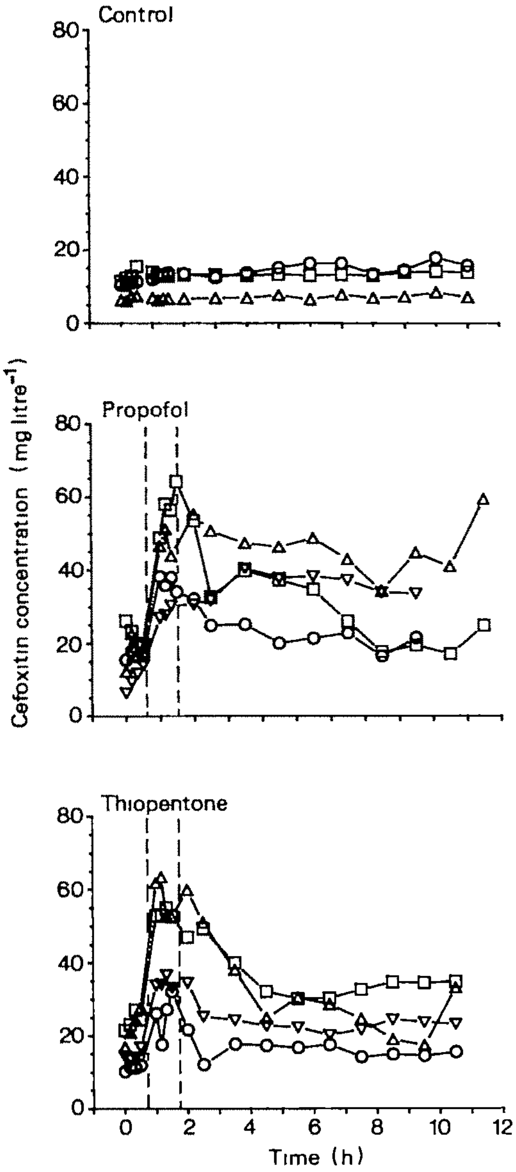

FIG. 1. Individual arterial blood concentrations of cefoxitin in three sheep in the control studies, and four in the propofol and four in the thiopentone anaesthesia studies. After a loading infusion of 22.6 mg min^{-1} for 15 min, cefoxitin was administered by constant rate infusion at 11.5 mg min^{-1} throughout the studies. In the control studies, the respective mean arterial blood concentrations of cefoxitin in the three animals were 13.7 (SD 2.1), 7.0 (0.6) and 13.3 (0.9) mg litre^{-1}; the respective renal venous concentrations were 4.2 (0.7), 2.2 (0.8) and 1.1 (0.4) mg litre^{-1}; respective renal extraction ratios of cefoxitin were 0.69 (0.03), 0.67 (0.14) and 0.92 (0.03) and the corresponding renal clearances of cefoxitin 0.66 (0.09), 0.91 (0.20) and 0.89 (0.16) litre min^{-1}. For the anaesthesia studies, the period of anaesthesia is indicated by the broken vertical lines.

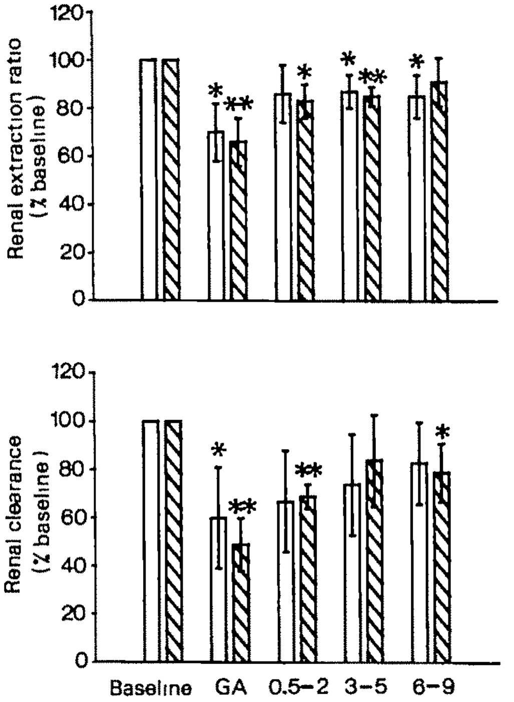

FIG. 2. The effects of propofol (open panels) and thiopentone (hatched panels) anaesthesia on renal extraction ratio and renal clearance of cefoxitin during constant rate infusion in the sheep. To facilitate comparisons between time periods, the individual mean values during the 30-min period immediately before anaesthesia have been assigned a value of 100% (baseline) and values during subsequent periods have been expressed as percentage mean and SD of this value. Test periods were observed during the last 30 min of a 70-min period of anaesthesia (GA), during early recovery (0.5–2 h), during mid recovery (3–5 h) and during late recovery (6–9 h). Statistical significance (two-tailed): *$P < 0.05$; **$P < 0.01$.

expressed as percentages of the corresponding baseline values. Two-tailed probabilities of $P < 0.05$ were considerably statistically significant.

RESULTS

Similar values were observed in the control studies and in the baseline periods of the anaesthesia studies. In the control studies, there were no significant cardiovascular changes caused by administration of cefoxitin and the blood concentrations of cefoxitin remained essentially constant throughout the entire study period (fig. 1). In marked contrast to the constancy of the control and baseline observations, anaesthesia with each anaesthetic agent caused the cefoxitin blood concentrations to increase abruptly, although a new steady state could not be determined in every case within the anaesthesia period (fig. 1). The overall mean arterial blood concentrations of the anaesthetic agents during this period were propofol 8.4 (SD 2.2) mg litre^{-1} and thiopentone 47 (21) mg litre^{-1}.

The mean cefoxitin renal extraction ratios during propofol and thiopentone anaesthesia were, respectively, 70 (12)% ($P < 0.05$) and 66 (10)% ($P < 0.01$) of their respective baseline values (fig. 2); the corresponding mean renal clearances of cefoxitin were 60 (22)% ($P < 0.05$) and 49 (11)% ($P < 0.01$) of their respective baseline values (fig. 2). During this period, the mean renal blood flow was reduced during thiopentone anaesthesia to a mean of 73 (9)% ($P < 0.05$) of baseline, but it was not changed significantly during propofol anaesthesia (mean 80 (20)%, of baseline values). Although mean arterial blood concentrations of propofol were less than 0.1 mg litre^{-1} by 2–3 h after anaesthesia, recovery to baseline values of the mean renal extraction ratio of cefoxitin after propofol anaesthesia was not observed within the recovery period, although renal clearance of cefoxitin was not significantly different from baseline by the mid recovery period. The mean arterial blood concentration of thiopentone 4 h after anaesthesia was 8.9 (1.7) mg litre^{-1} or 21 (7)% of the individual mean values during anaesthesia. Recovery to baseline values of the mean renal extraction ratio of cefoxitin after thiopentone anaesthesia had occurred by the late recovery period and, although renal clearance of cefoxitin was not significantly different from baseline by the mid recovery period, it was again less than baseline in the late recovery period.

DISCUSSION

In the control studies and during the baseline period of the anaesthesia studies, the blood concentrations of cefoxitin remained essentially constant. During anaesthesia with propofol or with thiopentone, mean arterial blood concentrations of cefoxitin were approximately twice those immediately preceding anaesthesia. This could have been caused by decreased rate of elimination, a decreased extent of tissue distribution or both. The study design used was not able to determine the effects of anaesthesia on distribution, but it was observed that both anaesthetic agents markedly decreased the renal extraction ratio and clearance of cefoxitin. Only thiopentone decreased the renal blood flow significantly [4]. Although a new steady state was not necessarily achieved in each animal within the anaesthesia period, the resultant errors for drug equilibration within the highly perfused kidneys was believed to be acceptably small.

Cefoxitin is excreted renally by both glomerular filtration and tubular secretion. It is known that its rate of elimination is decreased in the presence of renal dysfunction [7]. Similar effects were caused by anaesthesia. Although it is possible that the renal effects of anaesthesia were mediated, at least in part, through competition for secretion between renally excreted metabolites of the anaesthetics and cefoxitin—as has been reported, for example, to occur in the presence of probenecid [8, 9]—it is probable that propofol and thiopentone share the depressant effects of the volatile anaesthetic agents on renal function [10, 11] which have also been observed for thiopentone in kidney slices *in vitro* [12]. Such effects on renal blood flow and renal function, it would seem, are common among general anaesthetic agents [10–17]; the differences between agents would seem to be mainly those of magnitude and time course. Although the clearance of propofol from the blood was much faster than that of thiopentone and the animals apparently recovered faster as judged by earlier extubation and standing, the effects of propofol on elimination of cefoxitin were not of a clearly shorter duration than thiopentone. This, too, suggests that the time course of effects of the anaesthetics may have been regulated by recovery of the same metabolically active process in the renal tubules.

The widespread use of propofol has prompted the need for further studies of its full range of pharmacological properties, including its effects on regional blood flow and on the kinetics of biologically relevant substances. Although the renal effects of these agents do not appear to be as great as those of the volatile anaesthetic agents, they are nevertheless appreciable, so that the kinetics of pharmacotherapeutic agents may be altered for many hours after apparent recovery from anaesthesia. Analogous studies of the effects of propofol and thiopentone on the regional pharmacokinetics of pethidine have been reported separately [18].

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EFFECTS OF PROPOFOL AND OF THIOPENTONE ANAESTHESIA ON THE REGIONAL KINETICS OF PETHIDINE IN THE SHEEP

L. E. MATHER, D. G. SELBY AND W. B. RUNCIMAN

SUMMARY

We have examined the extraction ratios, net fluxes and clearances of pethidine by the liver, kidneys and hindquarters in sheep before, during and after continuous anaesthesia (70 min) with propofol or thiopentone. Before anaesthesia, the overall mean respective regional pethidine extraction ratios were 0.98 (SD 0.01), 0.20 (0.06) and 0.44 (0.13), the corresponding net fluxes were 47 (7), 5 (2) and 20 (10) % dose min^{-1} *and the clearances 1.44 (0.22), 0.17 (0.07) and 0.80 (0.39) litre* min^{-1}. *During propofol anaesthesia, arterial blood concentrations of pethidine approximately doubled (*$P < 0.05$*), mean pethidine hepatic extraction ratio was unchanged, flux was increased to 145 (20) % and clearance decreased to 79 (10) % (*$P < 0.05$*) of baseline values; mean pethidine renal extraction ratio, flux and clearance were 73 (34), 112 (43) and 69 (31) % of baseline values; mean hindquarter pethidine extraction ratio decreased to 65 (25) % (*$P < 0.05$*) of baseline values. During thiopentone anaesthesia, arterial blood concentrations of pethidine approximately doubled (*$P < 0.01$*), mean pethidine hepatic extraction ratio was 97 (2) % of baseline values and flux and clearance were unchanged, mean pethidine renal extraction ratios, flux and clerance decreased to 37 (21), 54 (18) and 27 (19) % (all* $P < 0.05$*) of baseline values and mean pethidine hindquarter extraction ratio was 81 (20) % of baseline values. In spite of only modest changes in hepatic and renal blood flow during anaesthesia, blood concentrations of pethidine doubled and pethidine kinetics were disturbed for several hours after anaesthesia. Overall, however, the changes were of smaller magnitude and shorter duration than those that have been described for anaesthesia with the volatile anaesthetic agents.*

KEY WORDS

Anaesthetics, intravenous: propofol, thiopentone. Analgesics: pethidine. Pharmacokinetics: pethidine.

It has been shown that anaesthesia with volatile anaesthetic agents decreases the hepatic and renal clearances of many drugs [1], including pethidine [2]. There does not appear to be any equivalent information on the effects of continuous anaesthesia with the i.v. anaesthetic agents, propofol and thiopentone, on regional drug clearance. This study reports the extraction ratios, net fluxes and clearances of pethidine by the liver, kidneys and hindquarters in sheep and the effects of continuous i.v. anaesthesia with propofol and with thiopentone on these variables.

METHODS

Studies were performed in three groups of sheep prepared with chronically implanted catheters so that the regional extractions of pethidine and the relevant regional blood flows could be determined. One group was studied without perturbations to obtain control values; the other two groups were studied before (baseline values), during (anaesthesia values) and after (recovery values) total i.v. anaesthesia with either propofol or thiopentone. The preparation of the animals and the methods used have been reported previously in detail [3]

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and the cardiovascular effects of propofol and of thiopentone anaesthesia are reported in a companion paper [4]; only those aspects relevant to the effects on pethidine regional kinetics are reported here.

Experimental design

At least 1 week before the intended studies, adult merino ewes (weight 33–63 kg) were prepared with polyethylene catheters so that the tips were in the right atrium, aortic arch, a right hepatic vein, the left renal vein and the posterior vena cava (distal to the site of entry of the renal veins) for infusion of drugs and for sampling arterial, hepatic, renal and hindquarter effluent blood. The group prepared for the control studies had an additional catheter placed under direct vision with its tip in the descending aorta distal to the renal arteries. Cardiac output was measured by thermodilution, and hepatic and renal blood flows were measured by Fick methods using bromsulphthalein (BSP) and hippuran, respectively. Hindquarter blood flow was determined in the control group of animals by an indicator dilution method with the BSP infused into the abdominal aorta and measured in the posterior vena cava with correction for recirculation.

On the day of each study, two-stage infusions of pethidine and the relevant indicator substances were started and, after a 60-min rest period, observations were made and appropriate blood samples were collected at predetermined intervals for at least 10 h. In the anaesthesia groups, after four sets of values were obtained 10 min apart for individual baseline measurements, anaesthesia was induced with either propofol 250–300 mg over 1 min ($n = 4$ sheep) or thiopentone 750 mg over 1 min ($n = 4$ sheep), a cuffed tracheal tube was inserted and the lungs ventilated to normocapnia with an $F_{I_{O_2}}$ of 0.4. Maintenance infusions of propofol 20–25 mg min^{-1} constant or thiopentone 25 mg min^{-1} decreasing to 10 mg min^{-1} over the first 30 min were continued for 70 min. The last 30 min of this period was observed as the anaesthesia period and measurements were made as for the baseline period. After the maintenance

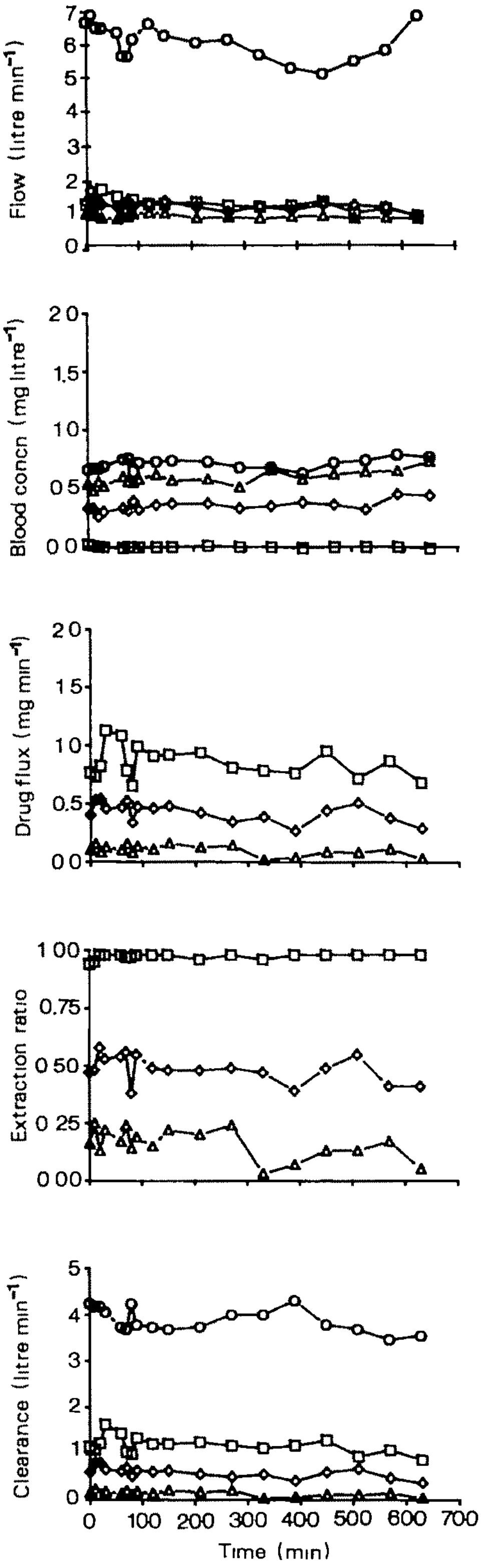

FIG. 1. Control values, obtained in one representative control study, for cardiac output and regional blood flows; arterial and regional blood concentrations of pethidine during constant rate infusion; regional fluxes of pethidine; regional extraction ratios of pethidine; regional clearances of pethidine. ○ = Cardiac output/arterial; □ = hepatic; △ = renal; ◇ = hindquarter/posterior vena cava.

TABLE I. *Regional kinetics during the continuous i.v. infusion of pethidine in three sheep during control studies over 11 h* (n = *18 samples*)

	Sheep		
	A	B	C
Cardiac output (litre min^{-1})	6.5 (0.5)	6.1 (0.5)	6.6 (0.4)
Hepatic blood flow (litre min^{-1})	1.34 (0.20)	1.21 (0.18)	1.34 (0.18)
Renal blood flow (litre min^{-1})	1.07 (0.10)	0.87 (0.06)	1.06 (0.09)
Hindquarter blood flow (litre min^{-1})	2.04 (0.24)	1.22 (0.16)	1.07 (0.23)
Blood concns of pethidine (mg litre^{-1})			
Arterial	0.68 (0.07)	0.72 (0.05)	0.86 (0.06)
Hepatic vein	0.011 (0.005)	0.021 (0.007)	0.05 (0.05)
Renal vein	0.53 (0.07)	0.61 (0.06)	0.72 (0.07)
Inferior vena cava	0.30 (0.05)	0.37 (0.05)	0.48 (0.09)
Extraction ratios of pethidine			
Hepatic	0.998 (0.007)	0.97 (0.01)	0.94 (0.06)
Renal	0.21 (0.08)	0.16 (0.07)	0.16 (0.09)
Hindquarter	0.56 (0.07)	0.49 (0.06)	0.44 (0.11)
Net flux of pethidine (% dose min^{-1})			
Hepatic	37 (7)	31 (5)	40 (5)
Renal	6 (2)	4 (1)	5 (3)
Hindquarter	28 (5)	16 (3)	26 (6)
Clearance of pethidine (litre min^{-1})			
Hepatic	1.34 (0.20)	1.18 (0.18)	1.26 (0.18)
Renal	0.25 (0.07)	0.14 (0.06)	0.18 (0.10)
Hindquarter	1.14 (0.19)	0.60 (0.12)	0.45 (0.20)
Total body	4.26 (0.51)	3.39 (0.25)	3.29 (0.22)

infusions were stopped, recovery was observed by repeating the measurements at 0.5, 1.0, 2, 3, 4, 5, 6, 7, 8 and 9 h. For subsequent statistical analysis, these were grouped into early (0.5–2 h), mid (3–5 h) and late (6–9 h) recovery periods.

Pharmacokinetic calculations

Pethidine hydrochloride was infused into the right atrium using a two-stage regimen to produce constant arterial blood concentrations. Loading doses (5.6 mg min^{-1} for 15 min) were followed immediately by maintenance infusions (2.7 mg min^{-1}) for the duration of the study. Individually calibrated syringes were used so that all dose rates were known accurately. Analysis of the blood concentration of pethidine was performed by solvent extraction followed by gas–liquid chromatography with nitrogen selective detection [5].

The mean total body clearance of pethidine was determined from the ratio of the maintenance infusion rate to the arterial blood concentration. While this value was calculated for comparative purposes for the periods during and after anaesthesia, it was uncertain if this calculation was accurate for these periods as it was uncertain that distribution equilibrium had re-occurred within the time frames examined [6]. The relevant regional net fluxes and clearances of pethidine were determined from the respective products of the blood flows and arteriovenous concentration differences and blood flows and extraction ratios. In previous studies, it had been observed that the total body clearance of pethidine was greater than could be accounted for by the sum of the measured visceral clearances [2]. In the present studies, therefore, we have measured the hindquarter net flux and clearance of pethidine to help account for the discrepancy by measuring the loss to a representative non-visceral region during the various time periods. In addition, to help quantitate any effects of anaesthesia on hepatic drug elimination capacity, the hepatic intrinsic clearances of pethidine were calculated from the ratios of hepatic clearance to (1 − hepatic extraction ratio) [7].

Statistical analysis

A longitudinal study design was used in the anaesthesia groups so that significant changes

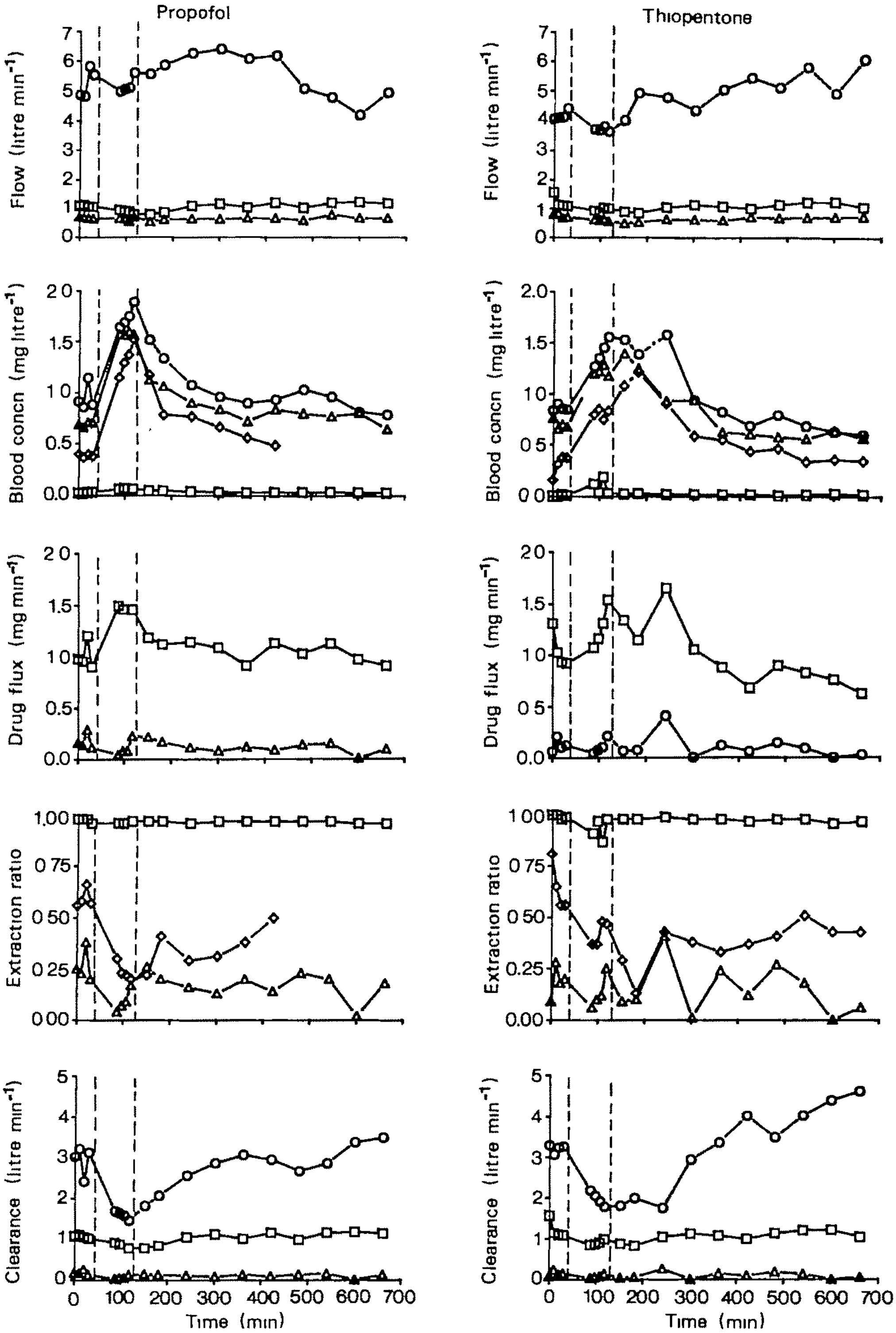
Propofol
Thiopentone
Flow (litre min^{-1})
0
1
2
3
4
5
6
7
Blood concn (mg litre^{-1})
0.0
0.5
1.0
1.5
2.0
Drug flux (mg min^{-1})
0.0
0.5
1.0
1.5
2.0
Extraction ratio
0.00
0.25
0.50
0.75
1.00
Clearance (litre min^{-1})
0
1
2
3
4
5
0
100
200
300
400
500
600
700
Time (min)

FIG. 2.

could be detected with small sample sizes. The respective mean value in the baseline period of each individual study was assigned a value of 100% and one sample *t* tests against this value were performed for each, expressed as percentage means and SD of the corresponding baseline values. Two-tailed probabilities of $P < 0.05$ were considered statistically significant.

RESULTS

Control studies

In this group, arterial and regional venous blood pethidine concentrations remained essentially constant throughout the study period, with no signs of decreasing systematically with time. From figure 1, it may be seen that extraction of pethidine occurred in the liver, kidneys and hindquarters; the regional kinetics of pethidine are summarized in table I. The summed fluxes by these regions accounted for approximately 67% of the dose. The majority of the remainder, it may be assumed, could be accounted for by extraction into other regions analogous to the hindquarters.

Propofol anaesthesia studies

In this group, the mean (SD) of the pethidine baseline hepatic kinetic parameters extraction ratio, net flux and clearance were, respectively, 0.99 (0.01), 44 (12)% dose min^{-1} and 1.53 (0.36) litre min^{-1}; the renal kinetic parameters extraction ratio, net flux and clearance were, respectively, 0.18 (0.08), 5 (1)% dose min^{-1} and 0.12 (0.05) litre min^{-1}; hindquarter extraction ratio was 0.39 (0.14). Anaesthesia with propofol caused the blood concentrations of pethidine to increase to approximately double their baseline values ($P < 0.05$) (fig. 2). At the same time, the mean hepatic extraction ratio for pethidine was unaltered, the hepatic net flux was increased to 145 (20)% and the mean hepatic clearance was decreased to 79 (10)% of baseline (both $P < 0.05$). The mean renal extraction ratio, net flux and clearance were not altered significantly (respectively, 73 (34)%, 112 (43)% and 69 (31)% of baseline). The mean hindquarter extraction ratio was decreased to 65 (25)% of baseline values ($P < 0.01$) (fig. 3). The overall mean hepatic intrinsic clearance of pethidine was not decreased with propofol anaesthesia, although it was clearly decreased in two of the four animals (table II).

Thiopentone anaesthesia studies

In this group, the mean (SD) of the baseline pethidine hepatic kinetic parameters extraction ratio, net flux and clearance were, respectively, 0.99 (0.01), 42 (17)% dose min^{-1} and 1.36 (0.14) litre min^{-1}; the renal kinetic parameters, extraction ratio, net flux and clearance were, respectively, 0.25 (0.08), 5 (1)% dose min^{-1} and 0.30 (0.17) litre min^{-1}; the hindquarter extraction ratio was 0.51 (0.18). Anaesthesia with thiopentone caused the blood concentrations of pethidine to increase to approximately double their baseline values ($P < 0.01$) (fig. 2). At the same time, the pethidine mean hepatic extraction ratio, hepatic net flux and clearance were not significantly different from baseline values (respectively, 97 (2)%, 176 (100)% and 109 (79)%), the mean renal extraction ratio, net flux and clearance were 37 (21)%, 54 (18)% and 27 (19)% of baseline (all $P < 0.05$) and the mean hindquarter extraction ratio was 81 (20)% of baseline (fig. 3). The mean hepatic intrinsic clearance of pethidine was decreased in each animal during thiopentone anaesthesia (table II).

DISCUSSION

From comparable studies in sheep we have reported that anaesthesia with 1.5% halothane ($F\text{I}_{\text{O}_2}$ 0.4) decreased the hepatic clearance of pethidine by about 40% and virtually abolished its renal clearance. Similar effects occur with 1% halothane, 2% enflurane and 2% isoflurane anaesthesia [8]. In the present studies, propofol anaesthesia decreased the mean hepatic clearance of pethidine in each of the four animals tested; thiopentone did so in three of the four animals tested (table II). During anaesthesia with each agent, the individual reductions in hepatic clearance of pethidine were greater than the reductions in the hepatic extraction ratio of pethidine, the predominant effect being mediated by decreases in hepatic blood flow. However, the hepatic intrinsic clearance of pethidine, despite being extremely high in the sheep, was also decreased by

FIG. 2. Regional blood flows and clearances of pethidine. Effects of propofol (left) and thiopentone (right) anaesthesia on regional pethidine blood concentrations in two representative anaesthesia studies. The period of anaesthesia was for 70 min, indicated by the vertical broken lines. ○ = Cardiac output/arterial; □ = hepatic; △ = renal; ◇ = hindquarter/posterior vena cava.

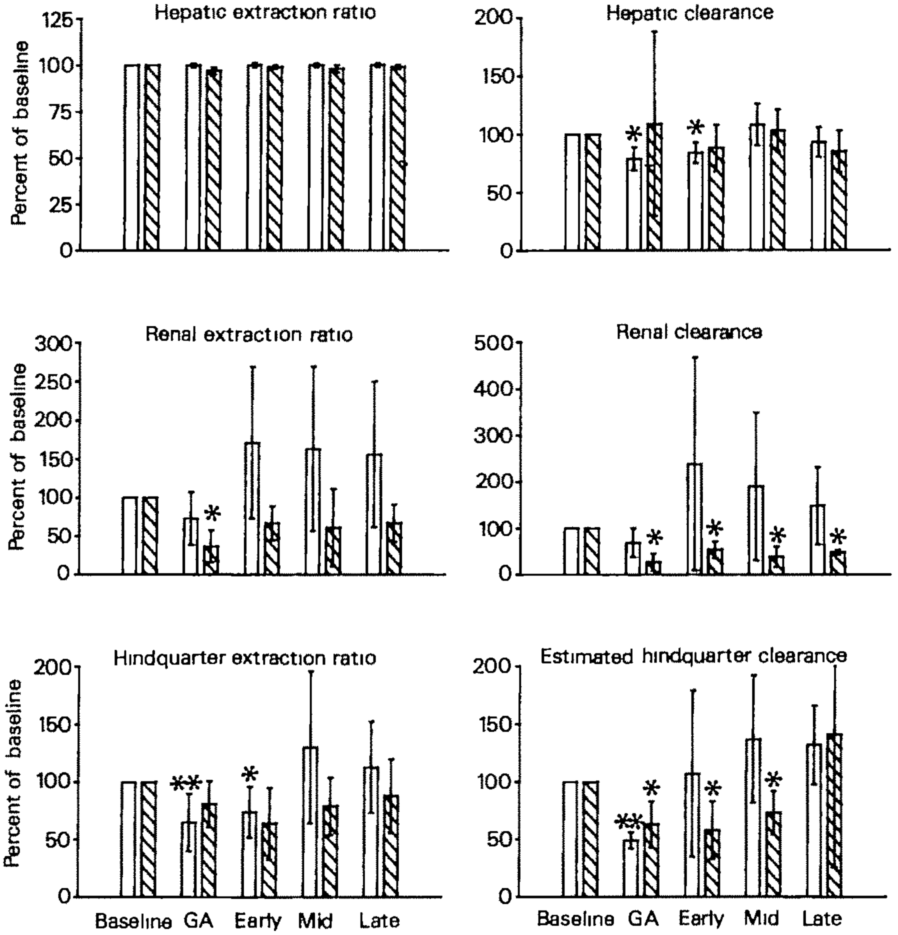

FIG. 3. Effects of propofol (open panels) and thiopentone (hatched panels) anaesthesia on pethidine hepatic extraction ratio and clearance, pethidine renal extraction ratio and clearance and pethidine hindquarter extraction ratio and estimated clearance assuming that hindquarter blood flow was 20 % of cardiac output in the sheep. To facilitate comparisons, the mean values during a 30-min control period were each assigned a value of 100 % (baseline) and the corresponding values during the subsequent test periods were expressed as the percent mean and SD of the baseline value. Test periods were observed during the last 30 min of a 70-min period of anaesthesia (GA), during early recovery after anaesthesia (0.5–2 h), during mid recovery after anaesthesia (3–5 h) and during late recovery after anaesthesia (6–9 h). Significant decreases (two-tailed) compared with baseline: $*P < 0.05$; $**P < 0.01$.

the anaesthetic agents in all but two of the eight studies, suggesting a depressant action of these anaesthetic agents on hepatic drug clearance independent of decreases in hepatic blood flow in these animals.

Renal clearance of pethidine was decreased to a greater extent than renal blood flow. Because negligible quantities of pethidine are excreted into the urine of sheep, it is probable that the measured renal clearance included both renal excretion and renal metabolism of pethidine. Thus these effects of the anaesthetic agents also were consistent with greater decreases in metabolic clearance of drug (i.e. enzyme function) than in blood flow.

Consistent with our previous observations, the total body clearances of pethidine in these sheep were greater than the sum of the measured clearances by the major visceral organs [2]. This discrepancy subsequently has been explained by unexpectedly high pethidine uptake into muscle

TABLE II. *Hepatic kinetics of pethidine in individual animals, before and during propofol anaesthesia (Studies 1–4) and during thiopentone anaesthesia (Studies 5–8). Values during anaesthesia are expressed as percentages of corresponding baseline values in the same animals before anaesthesia. Mean* (SD) *of four values except* † n = 3. *ER = Extraction ratio;* Cl = *clearance; I*Cl = *intrinsic clearance* (= Cl/*1 − ER*). * *Not determined because ER = 1.00 and thus I*Cl *was infinitely great; however, it is clear that I*Cl *was reduced during anaesthesia because ER was decreased*

	Study No.							
	1	2	3	4	5	6	7	8
Hepatic blood flow								
Baseline period (litre min^{-1})	1.72 (0.18)	1.39 (0.14)	1.09 (0.04)	1.91 (0.35)	1.36 (0.11)	1.36 (0.22)	1.60 (0.89)	1.23 (0.23)
Anaesthesia period (% baseline)	91 (5)	76 (11)	81 (6)	71 (9)	228 (76)	79 (6)	61 (12)	78 (6)
Pethidine kinetics								
Baseline period								
ER	0.99 (0)	0.99 (0)	0.98 (0.01)	0.99 (0)	1.00 (0)	0.96 (0.02)	0.98 (0.02)	0.99 (0.01)
Cl (litre min^{-1})	1.70 (0.18)	1.44 (0.07)	1.06 (0.04)	1.90 (0.35)	1.36 (0.11)	1.30 (0.22)	1.56 (0.87)	1.22 (0.23)
I*Cl* (litre min^{-1})	194 (94)	170 (58)†	41 (10)	221 (64)	*	62 (78)†	74 (50)	233 (186)
Anaesthesia period								
ER (% baseline)	100 (0)	100 (1)	99 (1)†	99 (0)	99 (1)	98 (1)	99 (2)†	94 (5)
Cl (% baseline)	92 (5)	73 (11)	80 (7)	70 (8)	226 (77)	78 (5)	58 (12)	74 (5)
I*Cl* (% baseline)	136 (27)	103 (47)	57 (4)	31 (6)	*	38 (31)	41 (27)	11 (10)

and fat of sheep both *in vivo* and *in vitro*, the former being consistent with metabolism of pethidine [9]. In these studies, the extraction of pethidine by the hindquarters, measured to assess the extent of pethidine uptake by a defined extra-visceral region [8], showed substantial extraction ratios (overall mean baseline value 0.44 (SD 0.14) ($n = 7$)). Thus, with a blood flow of approximately 1 litre min^{-1}, uptake into the hindquarters accounts for an appreciable portion of the dose of pethidine and of its total body clearance. Similar extraction ratios would be expected in analogous anatomical regions such as the fore-quarters, body trunk and chest wall, with clearances in proportion to their regional blood flows. That this extraction of pethidine was not caused only by filling of a slowly equilibrating tissue is indicated by the constancy of the hindquarter venous effluent blood concentrations, extraction ratios and clearances of pethidine throughout the control studies. The hindquarter extraction ratio of pethidine during anaesthesia was 65 % of baseline with propofol and 81 % of baseline with thiopentone. Overall, the mean summed hepatic and renal blood flows decreased less during anaesthesia than did cardiac output. Therefore, during anaesthesia, blood flow to the non-visceral regions represented by the hindquarters would have been decreased. Thus hindquarter net flux and clearance of pethidine must have decreased by at least the same percentage decrease as that in extraction ratio. Recovery from propofol anaesthesia was faster than from thiopentone (as in the human) and this was reflected in the earlier recovery of the animals to standing and moving about in their metabolic crates, thereby presumably increasing, and altering, the hindquarter blood flow and clearance of pethidine.

During anaesthesia, some of the increase in blood concentrations of pethidine may have occurred because of a contracted volume of distribution of pethidine arising from the redistribution of cardiac output. This would result in a minimally decreased or even increased net flux of pethidine in the face of a decreased corresponding clearance. The relative contributions of altered clearance and distribution are difficult to gauge accurately using a constant rate infusion experimental design, but the relative changes in clearance and flux give some idea. On this basis, the values during anaesthesia would seem to be about 33–50 % of the corresponding baseline values. Accurate determination of differences in the volumes of distribution of pethidine would necessitate different experimental design, perhaps involving a step change in the pethidine dose regimen. In fact, there is evidence of a contracted distribution volume in our previous report on the effects of halothane anaesthesia on pethidine disposition. Others have reported recently that a change in apparent volume of distribution occurs with propranolol during propofol anaesthesia [10]. Although there may be concomitant changes in the binding of pethidine in blood, which is approximately 50% in sheep blood *in vitro* at these concentrations, the effect on blood concentrations of pethidine *in vivo* would be small because of buffering by the volume of distribution [11].

For pethidine for which, in the sheep, regional clearances are determined predominantly by regional blood flow, pharmacokinetic drug interactions through the effects of anaesthetics on regional blood flow would appear to be inevitable. However, anaesthetic agents can affect also the energy dependent enzymic mechanisms responsible for regional metabolism or renal tubular secretion, or both, as reflected by changes in intrinsic clearance. Such effects have been observed for nearly all anaesthetic agents [1, 2, 8, 12–14].

In spite of only modest changes in hepatic and renal blood flow during anaesthesia, blood concentrations of pethidine doubled and pethidine kinetics were disturbed for several hours after anaesthesia. Overall, however, the changes were smaller and of shorter duration than those that have been described for anaesthesia with the volatile anaesthetic agents.

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EFFECT OF GENERAL ANAESTHESIA ON WHOLE BODY PROTEIN TURNOVER IN PATIENTS UNDERGOING ELECTIVE SURGERY

F. CARLI, V. RAMACHANDRA, J. GANDY, H. MERRITT, G. C. FORD, M. READ AND D. HALLIDAY

SUMMARY

To determine if general anaesthesia alone or in conjunction with surgery alters body protein turnover, we studied six healthy, unpremedicated females undergoing elective total abdominal hysterectomy. Changes in protein metabolism, synthesis and breakdown were estimated by an isotope dilution technique using a continuous infusion of the stable isotope tracer, L-[1-^{13}C]leucine, before anaesthesia (4 h), during anaesthesia alone (1 h), during anaesthesia and surgery (1 h) and in the recovery period (2 h). General anaesthesia comprised thiopentone, pancuronium, enflurane (1 MAC) and oxygen-enriched air. An isotopic steady state in plasma ^{13}C-α-ketoisocaproate (^{13}Cα-KIC) and expired ^{13}C-carbon dioxide were obtained during the four periods. Collections of plasma and expired air were made during the steady state periods and plasma α-KIC enrichment measured to indicate precursor pool labelling from which leucine flux (equal to protein breakdown in the post-absorptive state) and oxidation were calculated, and whole body protein synthesis was derived. Whole body protein breakdown did not change with anaesthesia, but decreased with both surgery and during the acute recovery period ($P < 0.05$). Protein synthesis did not change with anaesthesia and surgery, but decreased significantly after surgery ($P < 0.05$).

KEY WORDS
Metabolism · protein.

Elective surgery is associated with postoperative negative nitrogen balance and increased plasma concentration of branched chain amino acids [1]. These changes must reflect an increase in whole body protein breakdown, a decrease in synthesis, or both [2]. Factors such as preoperative nutritional status, immobilization, intensity of trauma, substrate administration and anaesthetic techniques should be considered, but, whilst the contribution of some of these factors is well recognized, the effect of anaesthesia on protein metabolism has not received attention in surgical studies.

Anaesthesia alone by the *in vitro* administration of halothane has been reported to result in a small but reversible decrease in tissue protein synthesis [3]. More recently, an investigation on the effect of halothane and nitrous oxide anaesthesia in dogs showed that leucine oxidation and whole body protein breakdown increased, while protein synthesis was depressed [4].

We have examined the acute effect of general anaesthesia alone followed by anaesthesia and surgery on whole body protein turnover in patients undergoing elective surgery of moderate intensity.

PATIENTS AND METHODS

We studied six females (mean age 44 yr (range 38–50 yr), mean weight 65 (50–75) kg and mean body mass index 25.3 (21.4–26.7) kg m^{-2}) undergoing elective total abdominal hysterectomy for menorrhagia. None of the patients was suffering from endocrine disease or receiving medication.

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The study was approved by the local Ethics Committee and informed consent was obtained from each patient.

Anaesthesia

None of the patients received any premedication. General anaesthesia was induced with thiopentone 5 mg kg^{-1}, the trachea was intubated following administration of pancuronium bromide 0.1 mg kg^{-1} and the lungs were ventilated to normocapnia with oxygen-enriched air ($F_{I_{O_2}}$ = 35%).

Nitrous oxide was not used in this study, as it has the same molecular weight as carbon dioxide and thus interferes with the isotope ratio measurement of expired air ^{13}C-carbon dioxide. Anaesthesia was maintained with an end-expiratory enflurane concentration of 1.67 ± 0.13% (1 MAC) throughout the study and a dose of papaveretum 10 mg was administered i.v. before skin incision. Normal saline 0.9% was infused i.v. during anaesthesia, surgery and in the recovery period at a rate of 6 ml kg^{-1} h^{-1}. Blood transfusion was not required during surgery or recovery.

ECG, non-invasive systemic arterial pressure, end-tidal concentrations of carbon dioxide (Hewlett–Packard) and enflurane (Emma, Engstrom), inspired concentration of oxygen, oxygen saturation, aural canal temperature and train-of-four were monitored and recorded during anaesthesia and surgery. In three of the subjects, a cannula was inserted into the radial artery after induction of anaesthesia and heparinized blood samples taken to measure pH and standard bicarbonate during anaesthesia, surgery and recovery. Attempts were made to keep the patients warm during the studies. Ambient temperature and relative humidity in the operating theatre were maintained at 23.5 ± 0.8 °C and 55 ± 5%, respectively.

Following a period of 1 h of general anaesthesia, surgery was then started which lasted 1 h. The operations were performed by the same surgeon at the same time of the day on each occasion.

Following removal of the tracheal tube, the patients were transferred to the recovery room where they remained for 2 h; here, pain relief was achieved with papaveretum 5–10 mg administered i.v. as required.

Isotopes

L-[1-^{13}C]Leucine (99% 1-^{13}C) was obtained from Tracer Technologies (Newton, Ma, U.S.A.) and sodium bicarbonate (99% ^{13}C) from Cambridge Isotope Laboratories (Cambridge, Ma, U.S.A.).

All patients were studied on the day of surgery, at 08:00 after fasting approximately 12 h overnight (mean 11 h, range 10–13 h). A superficial vein in the dorsum of the hand was cannulated and the cannula kept patent with heparinized saline. A second superficial vein in the contralateral arm was cannulated to provide access for the infusion of L-[1-^{13}C]leucine. Blood and expired air samples were collected before the infusion to determine baseline carbon-13 enrichment. Primed doses of ^{13}C-$NaHCO_3$ 0.08 mg kg^{-1} and L-[1-^{13}C]leucine 0.5 mg kg^{-1}, prepared in the hospital pharmacy, were administered and followed immediately by a continuous infusion of L-[1-^{13}C]leucine 0.5 mg kg^{-1} which was continued throughout anaesthesia, surgery and recovery for a total of 8 h. Two hours after the start of the infusion of isotope, when the tracer was assumed to have reached an isotopic steady state, venous blood and expired air samples were collected every 15 min for the remainder of the study. Each subject lay quietly on the bed for 4 h before anaesthesia and was then transferred to the operating theatre.

A schematic representation of the procedure is shown in figure 1. Each blood sample collected before and during the infusion was transferred immediately to a heparinized tube and centrifuged at 4 °C. The plasma obtained was stored at −70 °C until α-ketoisocaproate (α-KIC) enrichment was measured. Expired air samples were collected in a 2-litre latex bag and transferred immediately to 20-ml Vacutainers (Beckton, Dickinson) to await ^{13}C-carbon dioxide isotope enrichment analysis.

During artificial ventilation, expired gases were

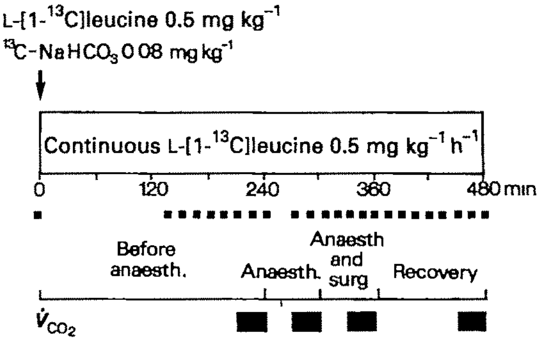
L-[1-^{13}C]leucine 0.5 mg kg^{-1}
^{13}C-$NaHCO_3$ 0.08 mg kg^{-1}
Continuous L-[1-^{13}C]leucine 0.5 mg kg^{-1} h^{-1}
0
120
240
360
480 min
Before anaesth.
Anaesth.
Anaesth and surg
Recovery
$\dot{V}_{CO_2}$

FIG. 1. Time course of the infusion of isotope and collection of plasma and expired air samples (■) during the four periods.

collected by means of a one-way valve into a 5-litre bag.

Production of carbon dioxide ($\dot{V}\text{CO}_2$) was measured by indirect calorimetry: expired air was collected for three periods of 3 min each and the expired volume ($\dot{V}\text{E}$) and the mixed expired concentration of carbon dioxide ($F\bar{\text{E}}_{\text{CO}_2}$) were measured by a dry gas meter (Parkinson & Gowan) and an infra-red gas analyser (Hewlett-Packard). Both instruments had been calibrated previously. During anaesthesia and surgery, measurements of $\dot{V}\text{CO}_2$ were performed 30 min after tracheal intubation and 30 min after surgical incision. In the recovery period the measurements were obtained during the last 45 min of infusion of leucine, when patients were rousable and co-operative.

Analytical methods

Whole body leucine kinetics were calculated by conventional isotope dilution practice using a two-pool stochastic model [5] during steady state conditions obtained at each phase of the studies. Plasma enrichment of α-KIC was used as the basis for calculating both flux and oxidation of leucine [6]. Thus, under steady state conditions, leucine flux (Q) is defined by the formula:

$$Q = S + O = B + I \qquad (1)$$

where S is the rate at which leucine is incorporated into body protein, O is the rate of oxidation of leucine, B is the rate at which unlabelled leucine enters the free amino acid pool from endogenous protein breakdown, and I is the rate of dietary intake or the rate of infusion of ^{13}C-leucine (μmol kg^{-1} h^{-1}) or both.

Inspection of equation (1) indicates that, when studies are conducted after absorption, flux is equal to breakdown. Both plasma α-KIC enrichment and concentration were determined by chemical ionization selected-ion monitoring gas chromatography–mass spectrometry using keto-valeric acid as internal standard. Expired breath ^{13}C-carbon dioxide enrichment was determined on the day of the study by means of isotope ratio mass spectrometry and used to calculate leucine oxidation. A factor of 0.81 was applied to account for the fraction of ^{13}C-carbon dioxide released by ^{13}C-labelled leucine oxidation but retained within slow turnover rate pools of the body [5].

Enrichment of plasma α-KIC during infusion of ^{13}C-leucine has been used to determine whole body leucine kinetics. This steady state reciprocal pool model is considered to provide a more precise representation of intracellular precursor pool enrichment than leucine itself [7, 8].

Plateau enrichment for both plasma α-KIC and expired carbon dioxide during the four periods (control, anaesthesia, surgery and recovery) exhibited a coefficient of variation of less than 4 % in all cases. The control mean value (range) was 1.82 (1.06–3.04) %, that during anaesthesia 2.8 (1.22–4.1) %, during surgery 2.0 (1.2–3.3) % and during recovery 3.1 (1.0–8.2) %. Plateau enrichment and concentration of α-KIC of one of the patients studied are presented in figure 2.

Statistics

Data are presented as means (SD). Differences between whole body protein kinetics during anaesthesia, surgery and recovery were deter-

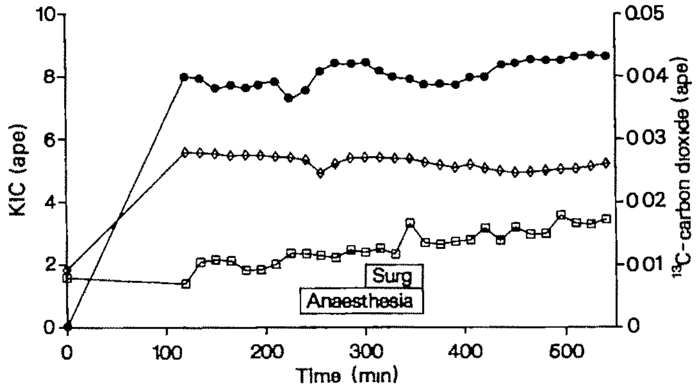

FIG. 2. Plateau enrichment, expressed in atom percent excess (ape), of ^{13}Cα-KIC (●) and ^{13}C-carbon dioxide (◇), and concentration of total α-KIC (□) during the 8-h infusion of isotope in one patient.

TABLE I. *Mean (SD) measurements of cardiovascular status, body temperature, production of carbon dioxide and concentration of α-ketoisocaproate (α-KIC) during the four phases* (n = 6). $*P < 0.05$ *compared with control*

	Control period	Anaesthesia	Anaesthesia and surgery	Recovery
Heart rate (beat min^{-1})	88 (9)	96 (12)	103* (13)	98 (15)
SAP (mm Hg)	125 (12)	111 (10)	128 (8)	121 (17)
Aural canal temp. (°C)	36.8 (0.7)	36.6 (0.4)	36.5 (0.5)	36.9 (0.4)
$\dot{V}CO_2$ (ml min^{-1})	168 (26)	153 (24)	156 (23)	176 (20)
[α-KIC] (μmol $litre^{-1}$)	20.7 (6.1)	18.4 (4.3)	22.7 (7.9)	21.4 (6.3)

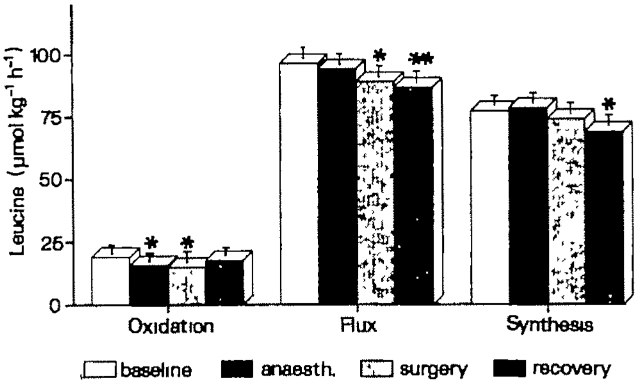

FIG. 3. Changes in leucine oxidation, flux and synthesis during anaesthesia, surgery and recovery. Compared with baseline: $*P < 0.05$; $**P < 0.01$.

mined using the two-tailed Student paired *t* test. Statistical significance was accepted at $P < 0.05$.

RESULTS

Mean duration of surgery was 58 min (56–63 min); mean operative blood loss was 235 ml (210–262 ml). Mean values of systemic arterial pressure, heart rate, core temperature recorded, $\dot{V}CO_2$ and concentration of α-KIC recorded during the steady states, before and during 1 h of general anaesthesia, 1 h of surgery and 2 h of recovery are presented in table I. There was a transient increase in heart rate during anaesthesia, but a significant increase occurred only during surgery. No significant changes in systemic arterial pressure occurred throughout the study. $\dot{V}CO_2$ decreased during anaesthesia and surgery by 8% compared with the preoperative values, but increased during the recovery. No significant changes in concentration of α-KIC occurred.

Mean (1 SD) arterial pH was 7.38 (0.02) during anaesthesia, 7.39 (0.02) during surgery and 7.37 (0.03) during the recovery period. Mean (1 SD) standard bicarbonate was 26 (1.8) mmol $litre^{-1}$ during anaesthesia, 25 (1.2) mmol $litre^{-1}$ during surgery and 24.8 (1.5) mmol $litre^{-1}$ in the recovery period. Oxygen saturation exceeded 95% throughout the study.

Leucine flux/breakdown during anaesthesia alone did not change in the patients studied, but decreased during surgery and during the first 2 h of recovery by approximately 7 and 10%, respectively ($P < 0.01$) (fig. 3). When the mean change in leucine flux occurring during surgery was compared with that observed with anaesthesia alone, no significant difference was found.

Oxidation of leucine decreased significantly during anaesthesia and surgery ($P < 0.05$), but returned during recovery to preanaesthetic values. Whole body leucine rate of disappearance, an indicator of whole body protein synthesis plus oxidation, did not change with anaesthesia alone. During surgery there was a non-significant decrease in protein synthesis compared with the preoperative values, and this decreased by another 7% during the recovery period ($P < 0.05$).

DISCUSSION

Stable, non-radioactive isotopes have become more widely used in clinical research in recent times, especially for quantitative assessment of aspects of protein metabolism. This renewed interest has been stimulated both by the increased availability and diversity of stable isotope-labelled compounds and by improvements in mass spectrometric methods for quantitative analysis [9].

The present study showed that, during general anaesthesia supplemented with 1 MAC enflurane, leucine kinetics in unpremedicated patients undergoing elective surgery did not change. However, whole body protein breakdown decreased significantly during surgery ($P < 0.01$) and recovery ($P < 0.01$), while a significant reduction in protein synthesis occurred only during the recovery phase ($P < 0.05$).

Measurements of whole body protein turnover and assessment of protein synthesis and breakdown give a dynamic picture of the movement of proteins in the body compared with more conventional indicators of protein metabolism such as nitrogen balance or specific muscle degradation indicators such as urinary 3-methylhistidine or creatinine.

In the fasting state, the sole source of leucine for protein synthesis and oxidation is that derived from the breakdown of endogenous proteins. To obtain an *in vivo* estimation of whole body protein metabolism, an isotope dilution technique has been used which measures labelled [1-^{13}C]leucine [5]. The flux of L-[1-^{13}C]leucine represents the total movement of leucine into and from the plasma pool. Oxidation of leucine results in its conversion to ^{13}C-carbon dioxide and leucine flux minus oxidation provides, indirectly, the rate of protein synthesis—a method used recently to measure protein kinetics associated with elective surgery, burns, malignancy and parenteral nutrition.

Ideally, in the execution of tracer studies, a period of at least 2 h should elapse before any observed establishment of a "new isotopic plateau" is interpreted as representing a real metabolic change. In the present study, ethical constraints limited the period of anaesthesia before surgery to little more than 1 h. Also, this surgery was chosen to represent surgical trauma of moderate intensity in which the surgical procedure, when performed by the same surgeon, was completed in 1 h. Thus anaesthesia was of 2 h total duration with surgery superimposed during the second 1 h. If highly significant metabolic changes had occurred as a result of either anaesthesia or surgery, they must have occurred to quantitatively the same extent, but in opposing directions, to produce the results obtained during the periods of anaesthesia and anaesthesia and surgery. Studies reporting the effect of feeding or insulin therapy on leucine kinetics [10, 11] indicate that major metabolic events can be observed within 1 h, as reflected by changes in the tracer enrichment, although the "final" isotopic plateaux were not obtained for approximately 2 h after the intervention. It may be argued, therefore, that the current results do not provide absolute proof that they truly reflect metabolic events occurring during the studies. However, confidence that the results are valid is strengthened in that the coefficient of variation of plateau values for both expired ^{13}C-carbon dioxide and plasma α-KIC was less than 4% for each arm of the study.

Some concern has been expressed in the past about the possible changes in the size of the body bicarbonate pool causing excess production or retention of label in breath carbon dioxide. In the present study, arterial pH and standard bicarbonate did not change significantly at any time. Increased oxidation calculated during the recovery phase resulted exclusively from an increase in the total production of carbon dioxide rather than from any change in the bicarbonate pool size or carbon dioxide enrichment. This latter observation indicates that neither changes in the bicarbonate pool size nor differential retention of ^{13}C-carbon dioxide in slowly turning over components of that pool were responsible for the enhanced oxidation. Indeed, we have found that during 4–8 h infusion studies of this nature there was no significant increase in bicarbonate recovery, which is thus independent of the duration of its infusion over this time interval [12; Wenham and colleagues, unpublished data].

A gradual increase in α-KIC enrichment occurring during the study period, as shown in figure 2, could indicate either a reduction in flux or recycling of label. We do not have any evidence that the latter occurred during the time course of infusion, as shown by previous studies in which leucine was infused for a similar period [10, 11, 13]. The present results are in disagreement with the findings reported by Rennie and MacLennan [14], who showed 45% and 36% decreases in protein synthesis and leucine flux, respectively, after halothane anaesthesia. These authors studied patients undergoing cardiac surgery who received halothane anaesthesia. However, no details relevant to preoperative nutritional status, drug history, concentration of anaesthetic agent used or duration of anaesthesia were reported and it is therefore difficult to make direct comparisons with the present study. It is of interest that these authors observed a change in α-KIC enrichment soon after the administration of an opioid premedication. In contrast, the administration of benzodiazepine before surgery does not seem to disturb isotopic equilibrium [15]. Because of these findings, it was decided to study unpremedicated patients in the first instance and look solely at the effect of general anaesthesia on protein kinetics.

The role of anaesthetic agents in the metabolic abnormalities of surgery and their effect on protein metabolism are not clear. The relatively few studies undertaken have looked at the volatile agent halothane and have been carried out in cell culture or isolated organ preparations. These studies have reported conflicting results: halothane inhibited protein synthesis in human lymphocytes [16] and rabbit pulmonary macrophages [17], but had no effect on protein synthesis in neuroblastoma cells [18]. In isolated perfused lung [19] and liver [20] preparations, halothane reversibly inhibited protein synthesis in a dose-dependent manner. One study in the rat showed a depressant effect of two exposures of halothane, at an interval of 24 h, on albumin and transferrin synthesis [21], while another investigation also in rats exposed to different concentrations of halothane showed a reduction in lung and liver fractional rates of protein synthesis [22].

A report [4] on the effect of halothane anaesthesia on whole body leucine metabolism in dogs indicated results that differed from those reported in the current study; thus oxidation and flux of leucine increased significantly after 180 min of nitrous oxide–halothane anaesthesia, while non-oxidative disappearance of leucine (an indicator of whole body protein synthesis) was decreased by approximately 10%. The authors also reported significant changes in plasma concentrations of amino acids 30 min after induction of anaesthesia and speculated on possible causes for the increased oxidation of leucine such as an alteration in regulatory enzymatic system or a liberation of catabolic hormones. However, these changes reported with anaesthesia appeared to be insignificant when compared with the response to surgical stimulation.

Another difference between the present study and that of Horber and colleagues [4] was the duration of anaesthesia. Their sampling and the derived calculations were started 120 min after the beginning of anaesthesia and continued subsequently for 2 h. This methodology might present some limitations when applied to human studies, and it is not clear if the duration of anaesthesia is related to the changes in oxidation of leucine. Furthermore, because the isotope and anaesthetic agents were administered at the same time, the authors could not determine the time course of the onset of this response to the administration of the anaesthetic agents in these dogs. The significant changes in whole body protein flux and synthesis observed in this study during surgery and in the immediate postoperative period were not of great magnitude. A decrease in either synthesis or flux might be the result of depressed body metabolism, as demonstrated during the ebb phase following experimental trauma in rats [23]. It is not yet known if this occurs in humans.

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CARDIOVASCULAR AND RENAL HAEMODYNAMIC EFFECTS OF DOPEXAMINE: COMPARISON WITH DOPAMINE

H. STEPHAN, H. SONNTAG, H. HENNING AND K. YOSHIMINE

SUMMARY

We have studied the effects of dopexamine and dopamine on systemic and renal haemodynamics in 20 male patients undergoing elective coronary artery bypass surgery. Patients were allocated randomly to two groups ($n = 10$*) who were treated with incremental doses of either dopexamine 1, 2 and 4 µg kg*$^{-1}$ *min*$^{-1}$*, or dopamine 2.5 and 5 µg kg*$^{-1}$ *min*$^{-1}$*, each dose being maintained for 15 min. Measurements were performed before administration of the drug and at the end of the infusion period at each dose. Fentanyl and midazolam were used as anaesthetic agents. Renal blood flow was measured with the argon washin technique. Dopexamine 4 µg kg*$^{-1}$ *min*$^{-1}$ *produced an increase in cardiac index of 117% caused by a 65% reduction in afterload and an increase in heart rate by 61%. Dopamine 5 µg kg*$^{-1}$ *min*$^{-1}$ *caused a 40% increase in cardiac index as a result of an increase in stroke volume. Renal vascular resistance decreased more than systemic vascular resistance with dopamine. With dopexamine, the increase in renal blood flow (66%) was less than the increase in cardiac index, while renal vascular resistance and systemic vascular resistance declined to almost the same extent. The results show that dopexamine exerts systemic and renal effects mainly via stimulation of* β_2*-receptors. An action of dopexamine at renal* DA_1*-receptors could not be demonstrated in this study.*

KEY WORDS

Heart: dopamine, dopexamine, cardiac output. Kidney. blood flow. Surgery: coronary artery bypass.

Dopexamine hydrochloride is a new synthetic dopamine analogue with properties and receptor activities different from those of dopamine (table I). It acts as a strong agonist at β_2-adrenoreceptors and stimulates peripheral dopamine receptors; its potency at vascular DA_1-receptors is 33% that of dopamine and its activity at prejunctional DA_2-receptors is four to six times less. Dopexamine has no α-adrenergic and only weak β_1-adrenergic effects and inhibits active neuronal reuptake of catecholamines (uptake-1) [1, 2].

Dopexamine reduces systemic vascular resistance and thus afterload and this is followed by an increase in cardiac output; it has specific renal vasodilating properties, with only little direct and indirect positive inotropic and chronotropic effects [1, 3, 4]. This profile suggests dopexamine may be superior to dopamine in treatment of low cardiac output states, when the usefulness of the latter is often limited by vasoconstriction, excessive tachycardia and arrhythmias [5, 6].

The aim of this study was to investigate the effects of dopexamine on general and renal haemodynamics in patients about to undergo aorto-coronary bypass surgery and to determine if these effects are superior to those of dopamine in cardiac patients.

PATIENTS AND METHODS

We studied 20 male patients (ages 43–62 yr, weight 66–102 kg) undergoing elective coronary artery bypass surgery. The study was approved by the Göttingen University Human Subjects Review Committee and written informed consent was obtained from each patient. Patients were

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TABLE I. *Receptor activities of dopexamine and dopamine. – = No activity; (+) = weak; + = mild; + + = moderate; + + + = strong stimulation* [1–4]

Receptor	Dopexamine	Dopamine
DA_1	+ +	+ + +
DA_2	+	+ +
α	–	+ +
$β_1$	(+)	+ +
$β_2$	+ + +	+
Uptake-1 inhibition	+ + +	+ +

allocated randomly to one of two groups treated with either dopexamine (n = 10) or dopamine (n = 10). There were no significant differences in age, weight, body surface area and ASA physical status between the groups. No patient gave a history of congestive heart failure or valvular heart disease. Ejection fraction was greater than 0.4. None of the patients had either a history or clinical evidence of metabolic disorders, liver disease or renal impairment. All patients were receiving maintenance doses of calcium-channel blocking drugs and nitrates. Two patients in the dopexamine group and three patients in the dopamine group were treated with β-adrenoreceptor antagonists. The last doses of all drugs were administered in the morning of the operation. All patients were premedicated with flunitrazepam 2 mg orally and promethazine 50 mg i.m. 1 h before arrival in the anaesthetic room.

Catheterization procedure

Upon arrival in the anaesthetic room ECG leads (lead II) were attached. Using the Seldinger technique under local anaesthesia, the following catheters were positioned: a 20-gauge catheter connected to a Goodale-Lubin catheter (USCI, 6F) in the radial artery of the non-dominant hand to monitor arterial pressure and for blood sampling; a second Goodale-Lubin (USCI, 6F) via the right internal jugular vein into the right renal vein for measurement of blood flow and withdrawal of blood samples; a pulmonary artery catheter (Edwards quadruple thermodilution model No. 93A 131-7F) flow-directed via an antecubital vein into the pulmonary artery for measurement of pulmonary artery and wedge pressures and cardiac output; and a polyethylene catheter into the superior vena cava for administration of drugs and infusions. The positions of all catheters were confirmed radiologically. ECG, body temperature and vascular pressures (Statham P23IA) were monitored continuously and recorded simultaneously on a 10-channel chart recorder (Hellige, Freiburg).

Measurements and anaesthesia

Anaesthesia was induced with fentanyl 6 $\mu g\,kg^{-1}$ and midazolam 0.2 $mg\,kg^{-1}$ and maintained with fentanyl 0.15 $\mu g\,kg^{-1}\,min^{-1}$ and midazolam 3 $\mu g\,kg^{-1}\,min^{-1}$. Pancuronium 8 mg was administered to facilitate tracheal intubation and the lungs were ventilated with 30 % oxygen in air using a constant volume ventilator (Engström ER 300).

After induction of anaesthesia and a 15-min period of rest, control measurements were performed. Subsequently, incremental doses of either dopexamine 1, 2 and 4 $\mu g\,kg^{-1}\,min^{-1}$ or dopamine 2.5 and 5 $\mu g\,kg^{-1}\,min^{-1}$ were administered, each maintained for 15 min, and measurements were repeated at the end of the infusion period at each dose. The doses of dopamine and dopexamine were chosen on the basis of expected renal equipotency.

Renal blood flow (RBF) was measured using the argon washin technique (coefficient of variation ± 5 %), a modification of the Kety-Schmidt technique [7] which includes simultaneous blood sampling from the renal vein and the radial artery during a 5-min period of inhalation of a standard concentration of argon. Immediately before and after each measurement of RBF, arterial and renal venous blood samples were taken and analysed for haemoglobin concentration, oxygen saturation and content (CO-Oximeter IL 282 and Lex-O_2-Con, Instrumentation Lab.), blood-gas tensions (standard electrodes, Radiometer) and electrolyte concentrations (atom absorption spectrophotometry, Perkin Elmer 303).

Cardiac output was measured by thermodilution (Fischer BN 7206). Cardiac index (CI) was calculated by dividing cardiac output by the body surface area, and stroke volume index (SVI) by dividing CI by heart rate. Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were derived from standard formulae, and renal vascular resistance (RVR) was calculated by dividing mean arterial pressure (MAP) minus renal venous pressure by RBF.

Statistical analysis of the data obtained in each group was performed using the Wilcoxon matched-pairs signed-ranks test; $P < 0.05$ was considered significant.

TABLE II: *Dopexamine: cardiovascular and renal haemodynamic effects (mean* (SD)). *HR = Heart rate; SAP = systolic arterial pressure; DAP = diastolic arterial pressure; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; MPAP = mean pulmonary arterial pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; CI = cardiac index; SVI = stroke volume index; RBF = renal blood flow; RVR = renal vascular resistance.* $P < 0.05$ *compared with:* * *control;* † *2 μg kg*$^{-1}$ *min*$^{-1}$

	Control	Dose of dopexamine (μg kg^{-1} min^{-1})		
		1	2	4
HR (beat min^{-1})	59 (10)	67 (11)*	75 (17)*	95 (39)*†
SAP (mm Hg)	117 (20)	109 (20)	112 (19)	102 (12)*
DAP (mm Hg)	68 (12)	55 (15)*	55 (13)*	48 (9)*
MAP (mm Hg)	83 (15)	71 (15)*	71 (13)*	65 (11)*
RAP (mm Hg)	2.8 (1.9)	2.8 (1.9)	3.2 (2.0)	4.2 (2.7)
PCWP (mm Hg)	6.5 (3.1)	7.1 (3.0)	6.9 (2.4)	8.3 (2.0)
MPAP (mm Hg)	12.5 (5.0)	14.2 (5.2)	14 (4.6)	17.8 (3.1)
PVR (dyn s cm^{-5})	110 (59)	81 (35)*	74 (36)*	79 (27)*
SVR (dyn s cm^{-5})	1424 (228)	780 (238)*	706 (288)*	503 (148)*†
CI (litre min^{-1} m^{-2})	2.40 (0.49)	3.86 (0.87)*	4.29 (0.90)*	5.21 (1.17)*†
SVI (ml m^{-2})	42 (9)	58 (11)*	58 (11)*	58 (11)*
RBF ((ml/100 g) min^{-1})	314 (49)	442 (87)*	469 (109)*	521 (147)*
RVR (mm Hg/(ml/100 g) min^{-1})	0.26 (0.06)	0.15 (0.04)*	0.15 (0.05)*	0.12 (0.03)*

TABLE III. *Dopamine: cardiovascular and renal haemodynamic effects (mean* (SD)). *For abbreviations see table II.* $P < 0.05$ *compared with:* * *control;* † *2.5 μg kg*$^{-1}$ *min*$^{-1}$

	Control	Dose of dopamine (μg kg^{-1} min^{-1})	
		2.5	5
HR (beat min^{-1})	56 (7)	57 (13)	59 (13)
SAP (mm Hg)	108 (18)	126 (23)*	155 (19)*†
DAP (mm Hg)	61 (8)	65 (10)	76 (15)*†
MAP (mm Hg)	78 (12)	86 (16)*	101 (14)*†
RAP (mm Hg)	2.8 (1.0)	3.9 (2.0)*	5.1 (2.2)*
PCWP (mm Hg)	6.3 (2.3)	8.9 (3.5)*	12.5 (5.5)*†
MPAP (mm Hg)	12.3 (3.1)	16.3 (5.6)*	22.7 (12.8)*†
PVR (dyn s cm^{-5})	100 (28)	97 (30)	121 (96)
SVR (dyn s cm^{-5})	1230 (179)	1079 (190)*	1134 (191)
CI (litre min^{-1} m^{-2})	2.46 (0.35)	3.07 (0.36)*	3.45 (0.53)*†
SVI (ml m^{-2})	45 (8)	55 (10)*	60 (10)*
RBF ((ml/100 g) min^{-1})	309 (46)	445 (84)*	559 (88)*†
RVR (mm Hg/(ml/100 g) min^{-1})	0.24 (0.06)	0.19 (0.04)*	0.17 (0.04)*

RESULTS

Cardiovascular effects

With increasing doses of dopexamine (table II), heart rate increased significantly and almost linearly by up to 61% at 4 μg kg^{-1} min^{-1}. SVR declined in a dose-dependent manner, by 45% with the smallest dose and by 65% with dopexamine 4 μg kg^{-1} min^{-1}, which resulted in significant decreases in diastolic arterial pressure (DAP) (19% and 29%, respectively). While systolic arterial pressure (SAP) decreased significantly (−13%) only with the greatest dose, MAP declined less than DAP (−14%) with the smallest dose of dopexamine and remained essentially unchanged with increasing doses. Right atrial, mean pulmonary arterial and wedge pressures changed little during the entire study period, while PVR decreased by 26% with the low dose; increasing doses of dopexamine did not have any further effect. The marked reduction in afterload led to a 38% increase in SVI with the smallest dose, but increasing doses of dopexamine caused such a great increase in heart rate that, although

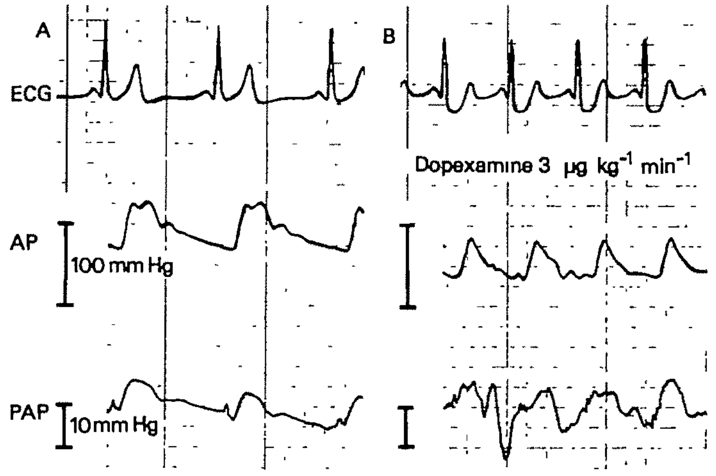

FIG. 1. ECG (lead II), arterial pressure (AP) and pulmonary artery pressure (PAP) of a patient before (A) and during (B) administration of dopexamine 3 μg kg^{-1} min^{-1}. Vertical scales: mm Hg.

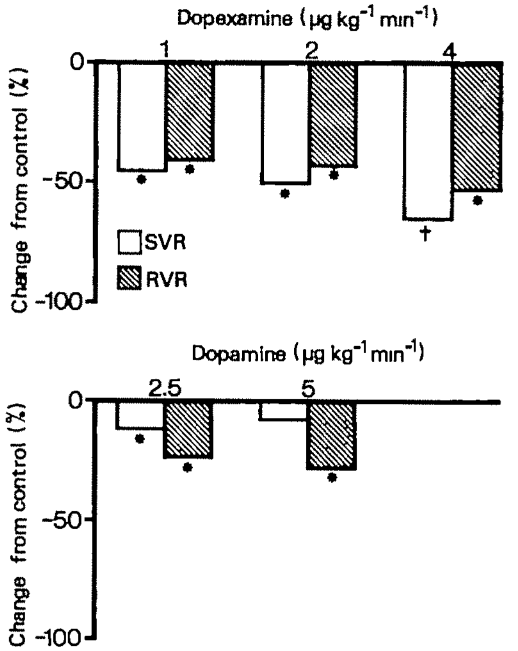

FIG. 2. Percentage changes in RVR and SVR compared with control values with increasing doses of dopexamine and dopamine. $P < 0.05$ compared with: * control; † all values.

CI was further increased by up to 117% with 4 μg kg^{-1} min^{-1}, SVI did not show any further changes.

The cardiovascular effects of dopamine (table III) differed substantially from those of dopexamine. While heart rate did not change with each dose of dopamine, SAP increased by 17% with 2.5 μg kg^{-1} min^{-1} and by 44% with 5 μg kg^{-1} min^{-1}. DAP and MAP increased, but only by 25% and 29%, respectively, with the high dose. There were marked dose-dependent increases in mean pulmonary arterial and wedge pressures, reaching almost twice the baseline values with 5 μg kg^{-1} min^{-1}, while PVR and SVR were influenced little. Heart rate remained unchanged throughout the study period; CI and SVI increased by 25% and 22%, respectively, with the low dose and by 40% and 33%, respectively, with the high dose of dopamine.

Two patients in the dopexamine group developed ST-segment suppression. In one, heart rate increased from 62 beat min^{-1} to 79 beat min^{-1} and MAP and DAP decreased from 70 and 50 mm Hg to 50 and 40 mm Hg, respectively, with 4 μg kg^{-1} min^{-1}. The second patient (fig. 1) had an increase in heart rate from 53 beat min^{-1} to 85 beat min^{-1} with dopexamine 3 μg kg^{-1} min^{-1}, accompanied by decreases in MAP and DAP from 90 and 68 mm Hg to 50 and 40 mm Hg, respectively.

Only one patient in the dopamine group developed ST-segment suppression with 5 μg kg^{-1} min^{-1}: at a stable heart rate of 55 beat min^{-1}, MAP increased from 85 to 105 mm Hg and DAP from 65 to 75 mm Hg. In three patients, the administration of dopamine 5 μg kg^{-1} min^{-1} was associated with arrhythmia: one patient developed atrial fibrillation, the second had supraventricular ectopic beats and the third, ventricular ectopic beats.

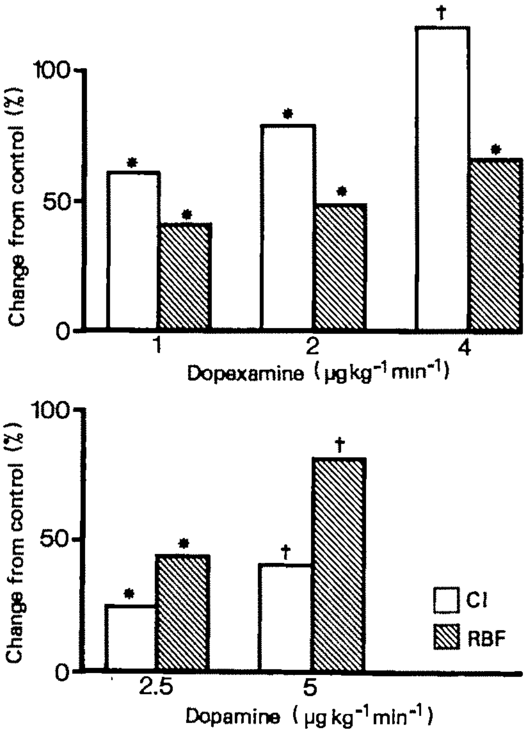

FIG. 3. Percentage changes in CI and RBF compared with control values, with increasing doses of dopexamine and dopamine. $P < 0.05$ compared with: *control; †all values.

Renal haemodynamics

In spite of their different effects on cardiovascular dynamics, both drugs affected RBF and RVR similarly (tables II, III).

Figure 2 illustrates the changes in RVR and SVR with increasing doses of dopexamine and dopamine expressed as percentages from control values. With dopexamine the ratio between RVR and SVR remained essentially unchanged, whereas increasing doses of dopamine had more effect on RVR than on SVR.

While increasing doses of dopexamine improved CI more than RBF, such that the renal fraction of CI (RBF/CI × 100) decreased from 13% to 10%, dopamine had more effect on RBF than on CI at increasing doses, with the renal fraction of CI increasing from 13% to 16% (fig. 3).

DISCUSSION

Haemodynamic effects

The results of this study demonstrate that both dopexamine and dopamine increased cardiac output, but via different mechanisms. Dopamine exerted its effects mainly by increasing stroke volume, attributed to activity at cardiac β_1-receptors [8, 9] resulting in increased contractility [9–11]. Dopexamine had little influence on stroke volume, but affected cardiac index by increasing heart rate and reducing SVR. Studies in dogs confirmed that the marked decrease in SVR is caused by stimulation of DA_1, DA_2 and β_2-receptors, while tachycardia is caused mainly by a β_2-mediated baroreceptor reflex [1–3].

In contrast with the data of the present study, Mousdale and colleagues [12] found an increase in SAP with dopexamine 1, 2 and 4 μg kg^{-1} min^{-1} in six healthy, awake volunteers. One may assume that awake subjects in a study are subjected to increased sympathetic tone, leading to α-receptor-mediated vasoconstriction in the peripheral vascular bed and thus attenuation of the vasodilating effects of dopexamine. On the other hand, patients in the present study were receiving maintenance doses of calcium-channel blocking drugs, which may have enhanced the vasodilating properties of dopexamine. Patients with congestive heart failure are known to have high plasma concentrations of noradrenaline [13]. Increased exposure of the failing heart to noradrenaline is an explanation for selective β_1-receptor downregulation, while selective β_2-receptors retain near full inotropic activity mediated through a β_2 population that is not significantly decreased [14]. Moreover, in chronic heart failure the baroreflex is generally blunted [15], which reduces the ability of dopexamine to stimulate the failing heart through baroreflex activation. However, because plasma concentrations of noradrenaline are increased, uptake-1 block by dopexamine may potentiate the cardiac effects of noradrenaline, and stimulation of cardiac β_2-receptors by dopexamine may become clinically important. All these mechanisms may lead to increased inotropy and decreased chronotropy with dopexamine in the failing heart compared with the actions of this drug in the non-failing heart [4]. This may also explain why arterial pressure remained relatively unaffected by dopexamine in patients with congestive heart failure [16, 17] whilst arterial pressure decreased in the present study, in which patients suffered from coronary heart disease but not from heart failure.

Mean pulmonary artery pressure and right and left atrial pressures remained unchanged and PVR decreased to a lesser extent than SVR, indicating that dopexamine had little influence on venous capacitance vessels and pulmonary circulation. On the other hand, dopamine produced significant dose-dependent increases in SAP, pulmonary arterial pressure and cardiac filling pressures, with little change in SVR or PVR. This may be attributed to the combined effects of dopamine at α-, β-, and dopaminergic receptors, even at the low dose of 2.5 µg kg^{-1} min^{-1} used in the present study. This is in contrast with the results of D'Orio and colleagues [9], who examined dose-dependent effects of dopamine and found that, with small doses (< 3 µg kg^{-1} min^{-1}), the effects of dopamine were limited to those resulting from stimulation of dopaminergic receptors. However, increases in cardiac output have been observed with doses even less than 3 µg kg^{-1} min^{-1} [10]. Shebuski, Smith and Ruffolo [18] observed that even low doses of dopamine increased PVR and pulmonary capillary wedge pressure in the propranolol pretreated dog; this was mediated by stimulation of postsynaptic vascular α-receptors in the pulmonary circulation. Thus patients might react differently to the same doses of dopamine, as was shown in hypertensive and aged patients [19, 20].

Adverse cardiovascular effects

In spite of their different haemodynamic effects, both drugs produced ST-segment depression indicating myocardial ischaemia. With dopamine, augmentation of contractility led to an increase in myocardial oxygen demand, which could not be met by an increase in coronary blood flow in one patient. Dopexamine increases oxygen demand by increasing heart rate, which may be counterbalanced by reduction in afterload and wall stress. It also decreased DAP and thus coronary perfusion pressure and by this mechanism may have induced myocardial ischaemia in two patients.

Myocardial ischaemia has been reported with dopamine [21] and with dopexamine [22]. Arrhythmias seem to occur significantly more often with dopamine than with dopexamine and are thought to be principally a β_1-receptor mediated effect. In animals, dopexamine was shown not only to be associated with a lower incidence of late arrhythmias after coronary occlusion than occurs with dopamine, but also to reduce the incidence of early arrhythmias to less than that seen without treatment [23]. The clinical observations of other authors and ourselves confirm these findings [16, 22].

Renal haemodynamics

Dopamine causes direct renal vasodilatation; an effect which is not blocked by β_2-receptor antagonists [24]. These findings were confirmed by a subsequent study in volunteers, who developed a 57% increase in RBF at subpressor doses of i.v. dopamine accompanied by a 48% increase in CI, such that the renal fraction of CI remained unchanged [25]. Rosenblum, Tai and Lawson [21] observed a 26% increase in CI and a 79% increase in RBF at doses between 2.1 and 5.8 µg kg^{-1} min^{-1}. This finding is consistent with the results of Abrahamsen and colleagues [11], who showed a 27% increase in CI and a 48% increase in RBF, together with an improvement of the renal fraction from 12% to 14%, with dopamine 5 µg kg^{-1} min^{-1} in patients with ischaemic heart disease.

The 44% and 81% increases in RBF with dopamine 2.5 and 5 µg kg^{-1} min^{-1}, respectively, obtained by the use of the argon washin technique in the present study, are within the range of values reported by other investigators. These improvements in RBF were caused by 25% and 40% increases in CI and by decreases in RVR by up to 28%, whereas SVR remained essentially unchanged (fig. 2); this is evidence for selective renal vasodilatory effects. The increase in CI was smaller than that in RBF (fig. 3), and MAP remained within the range of autoregulation, suggesting that systemic haemodynamic changes cannot solely account for improved renal haemodynamics.

With dopexamine there were greater increases in CI than in RBF (117% *vs* 66%, respectively, with 4 µg kg^{-1} min^{-1}) and renal fractions decreased from 13% to 10%, while SVR decreased more than RVR at all doses used, suggesting that the renal effects of dopexamine might be mediated by β_2-receptor stimulation and increase in CI, not necessarily by stimulation of renal DA_1-receptors. These results are in contrast with those of Magrini and colleagues [26] in eight hypertensive patients undergoing diagnostic renal vein catheterization. They observed a proportionally greater increase in RBF than in CI (20% *vs* 13%, respectively, with 3 µg kg^{-1} min^{-1}) and a significant reduction in RVR with increasing doses of dopexamine, while SVR remained unchanged. They concluded that dopexamine acted selectively at renal DA_1-receptors. These striking differences between those results and our data are difficult to explain, but might be related to the greater SVR in awake hypertensive patients or the enhanced responsiveness to stimulation of dopaminergic receptors as a result of greater numbers of free dopamine receptors and possible upregulation of their number in hypertensive subjects [19]. Mousdale and colleages [12] compared the effects of dopexamine, dopamine and dobutamine on renal blood flow in six volunteers using the PAH-clearance method. Dopexamine caused a progressive increase in RBF and a reduction in RVR, but to a lesser extent than dopamine at doses up to 5 μg kg^{-1} min^{-1}. From this the authors concluded that dopexamine had a specific effect on renal artery dopamine receptors, although they did not measure either CI or SVR, without which conclusions concerning specific dopaminergic activity cannot be drawn.

ACKNOWLEDGEMENT

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CEREBRAL EFFECTS OF SEVOFLURANE IN THE DOG: COMPARISON WITH ISOFLURANE AND ENFLURANE

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SUMMARY

The cerebral effects of sevoflurane were compared in dogs with those of enflurane and isoflurane. Initially, the minimum alveolar concentrations (MAC) of sevoflurane and enflurane were determined and the electroencephalographic (EEG) responses to increasing doses of sevoflurane (1.5, 2.0 and 2.5 MAC) or enflurane (1.5 and 2.0 MAC) in unparalysed animals were examined. Administration of sevoflurane was not associated with seizure activity at any concentration either during normocapnia (Pa_{CO_2} 5.3 kPa) or hypocapnia (Pa_{CO_2} 2.7 kPa), even in the presence of intense auditory stimuli. All dogs anaesthetized with enflurane demonstrated sustained EEG and motor evidence of seizure activity induced by auditory stimuli at concentrations of enflurane > 1 MAC, particularly during hypocapnia. In a separate group of dogs, the effects of increasing concentrations of sevoflurane and isoflurane (0.5, 1.5 and 2.15 MAC) were compared directly on arterial pressure, cardiac output and heart rate, cerebral blood flow and the cerebral metabolic rate for oxygen ($CMRO_2$) using the venous outflow technique. Sevoflurane, in common with isoflurane, had minimal effects on cerebral blood flow at the concentrations studied, but significantly reduced the $CMRO_2$ at end-tidal concentrations sufficient to produce a burst suppression pattern on the EEG (approximately 2.15 MAC). Both sevoflurane and isoflurane significantly decreased arterial pressure in a dose-dependent manner, but neither drug significantly altered cardiac output.

KEY WORDS

Anaesthetics, volatile: sevoflurane. Brain: blood flow, electroencephalography, oxygen consumption. Heart. cardiac output, heart rate. Arterial pressure. drug effects.

Sevoflurane is a volatile anaesthetic with a relatively low blood:gas partition coefficient of 0.60, compared with 1.41 and 2.40 for isoflurane and halothane, respectively [1]. Sevoflurane also has a pleasant, non-pungent odour which permits a smooth and rapid inhalation induction. These characteristics suggest that it might be useful for neurosurgical patients, in whom rapid induction and recovery are often desired. However, because sevoflurane is an ether anaesthetic, there is some concern that it may induce seizure activity, as does enflurane, particularly in the presence of hypocapnia which is used frequently during neurosurgical procedures. Seizure activity is known to increase the metabolic rate of the brain ($CMRO_2$), with attendant increases in cerebral blood flow (CBF) and intracranial pressure [2].

In a previous study we compared the effects in rabbits of increasing doses of sevoflurane and isoflurane on cortical cerebral blood flow, using the hydrogen clearance technique [3]. We demonstrated that the drugs did not alter cortical CBF. However, both drugs were administered in the presence of morphine and nitrous oxide and mean arterial pressure was maintained with angiotensin. The conditions were clearly different from those obtaining in clinical practice, and the haemodynamic effects of the drugs were not studied.

We therefore undertook the present study to compare the effects of sevoflurane, enflurane and isoflurane on the EEG, CBF, $CMRO_2$ and cardiovascular system in a dog model which allowed us to administer the drugs in a clinically relevant fashion.

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MATERIALS AND METHODS

All studies were undertaken following institutional Animal Care Committee review and approval.

Part one

Mongrel dogs of both sexes were anaesthetized by mask with either sevoflurane ($n = 5$) or enflurane ($n = 3$), the trachea was intubated and the animal positioned prone. The biparietal fronto-occipital EEG, femoral arterial pressure, ECG, end-tidal concentration of carbon dioxide ($F\text{E}'_{CO_2}$), end-tidal concentration of the volatile drug ($F\text{E}'_{drug}$) (Puritan Bennett infra-red volatile agent analyser) and oesophageal temperature (servo-controlled to 37.5 °C) were recorded continuously. The base of the animal's tail was shaved and MAC determined using the up-and-down method with a tail clamp as the stimulus [4]. $F\text{E}'_{drug}$ was increased or decreased by 10%, depending on the response of the animal. Twenty minutes was allowed for equilibration after each new $F\text{E}'_{drug}$ concentration was achieved. After MAC had been determined for a particular animal, the $F\text{E}'_{drug}$ was increased to 1.5 MAC and the animal allowed to equilibrate for 15 min. Auditory stimuli (repetitive, loud clanging of resonant metal containers) were then applied and the animal observed for the presence of either motor or EEG evidence of seizure activity. Hypocapnia (Pa_{CO_2} 2.7 kPa) was then induced and the sequence repeated. In the animals anaesthetized initially with sevoflurane, three $F\text{E}'_{drug}$ concentrations were studied in this manner: 1.5, 2.0 and 2.5 MAC. The animals receiving enflurane initially were studied only at 1.5 and 2.0 MAC. Following the observations of the animals at the greatest $F\text{E}'_{drug}$, the volatile anaesthetic was discontinued. At the first sign of "light anaesthesia" such as coughing or movement, the other volatile anaesthetic was introduced and increased to 1.5 MAC. After 30 min of equilibration with the new agent, the entire sequence of increasing concentrations, hypocapnia and auditory stimuli was undertaken again and the presence or absence of seizure activity recorded. The animals were killed humanely while still anaesthetized.

Part two

Mongrel dogs of both sexes were anaesthetized by mask with either sevoflurane ($n = 6$) or isoflurane ($n = 6$) on an alternating basis, the trachea was intubated and the animal paralysed with pancuronium. The lungs were ventilated with the volatile anaesthetic in oxygen. The animals were positioned prone and femoral arterial (for direct pressure monitoring and arterial blood-gas analysis) and venous cannulae (for cerebral venous outflow return) inserted. A pulmonary catheter was introduced via the right external jugular vein. Other monitors included temperature (servo-controlled to 37.5 °C), the EEG as described above, ECG, $F\text{E}'_{CO_2}$, and $F\text{E}'_{drug}$.

CBF was measured using the venous outflow technique. Briefly, following scalp incision, portions of the anterior skull were removed to expose diploic and ethmoidal veins which were occluded with bone wax or cauterized in order to exclude extracranial sources of blood. The sagittal sinus was exposed and a small plastic catheter inserted following systemic heparinization (3 mg kg^{-1} followed by 1 mg kg^{-1} h^{-1}). Sagittal sinus blood flow was measured using timed aliquots collected in triplicate. Global CBF was calculated from the sagittal sinus flow rate corrected for the weight of each dog's brain and the previously determined volume of brain known to be drained by the sagittal sinus [5].

$CMRo_2$ was calculated as the product of the arterial–sagittal sinus oxygen content difference and CBF. The arterial and venous blood oxygen contents were calculated from the oxyhaemoglobin saturation (IL 282 co-oximeter) and Pa_{O_2} (IL 813 blood gas analyser).

Following completion of the surgical preparation, all wounds were infiltrated with 0.25% bupivacaine and $F\text{E}'_{drug}$ reduced to 0.5 MAC (0.64% isoflurane or 1.05% sevoflurane). The animals were left undisturbed for 30 min before any measurements were made. The following variables were then recorded: mean arterial pressure (MAP), heart rate (HR), oesophageal temperature, cardiac output (CO), pulmonary artery systolic and diastolic pressures (PAS, PAD), pulmonary capillary wedge pressure (PCWP), CBF, $CMRo_2$, EEG, arterial blood-gases, and $F\text{E}'_{drug}$. $F\text{E}'_{drug}$ was then increased to 1.5 MAC and all variables recorded similarly after a 15-min equilibration period. Next, $F\text{E}'_{drug}$ was increased until burst suppression was noted on the EEG. Again, after a 15-min equilibration period, all variables were recorded. Finally, $F\text{E}'_{drug}$ was decreased to 0.5 MAC for 15 min and all variables recorded. The animals were killed humanely and the brains removed for weighing.

TABLE I. *Mean* (SD) *cerebral blood flow* (*CBF*), *cardiovascular variables*, Pa_{CO_2} *and volatile anaesthetic concentrations. Sevo.* = *Sevoflurane*; *Iso.* = *isoflurane*; *BS* = *burst suppression*; *MAP* = *mean arterial pressure*; *CO* = *cardiac output*; *PCWP* = *pulmonary capillary wedge pressure.* *P < *0.05 compared with 0.05 MAC*

	Concentration of volatile anaesthetic							
	0.5 MAC		1.5 MAC		BS		0.5 MAC	
	Sevo.	Iso.	Sevo.	Iso.	Sevo.	Iso.	Sevo.	Iso
CBF (ml/100 g min^{-1})	57 (14)	66 (13)	53 (10)	70 (25)	50 (14)	56 (21)	48 (18)	59 (21)
MAP (mm Hg)	117 (13)	129 (24)	93 (16)*	92 (20)*	76 (17)*	71 (15)*	114 (16)	128 (13)
CO (litre min^{-1})	1.9 (0.7)	1.5 (0.7)	1.4 (0.5)	1.7 (0.7)	1.5 (0.9)	1.3 (0.5)	1.9 (0.5)	1.8 (0.8)
PCWP (mm Hg)	3 (3)	5 (3)	3 (2)	7 (4)	5 (2)	9 (4)	5 (3)	7 (3)
Heart rate (beat min^{-1})	139 (39)	119 (16)	130 (38)	118 (13)	140 (28)	112 (15)	140 (20)	116 (18)
Pa_{CO_2} (kPa)	4.7 (0.4)	4.7 (0.4)	4.6 (0.4)	4.4 (0.5)	4.4 (0.4)	4.6 (0.3)	4.7 (0.4)	4.4 (0.4)
End-tidal concn (%)	1.0 (0.04)	0.66 (0.06)	3.14 (0.04)	1.9 (0.08)	4.49 (0.6)	2.8 (0.2)	0.66 (0.4)	1.1 (0.03)

Statistical analysis

Cardiovascular variables, CBF and $CMRo_2$ were compared within groups at the various FE'_{drug} by using a repeated measures analysis of variance followed by Dunnett's test where appropriate. $P < 0.05$ was considered statistically significant. Data are presented as mean (SD).

RESULTS

In all animals receiving sevoflurane in parts one and two, induction of anaesthesia was rapid and smooth. In part one animals, MAC of sevoflurane was 2.1 (SD 0.23) % and MAC of enflurane was 2.7 (0.36) %. Exposure to enflurane at both 1.5 and 2.0 MAC was associated with seizure activity (EEG and motor) during hypocapnia. This seizure activity could always be elicited by auditory stimuli and was nearly always sustained. In contrast, only one animal receiving sevoflurane demonstrated any evidence of seizure activity. This animal had first received enflurane and demonstrated only a brief EEG discharge associated with upper limb twitching, lasting less than 5 s during administration of 2.0 MAC sevoflurane during normocapnia, which was not elicted by auditory stimuli. Further attempts to elicit seizure activity in this animal, including the institution of hypocapnia and application of auditory stimuli, were unsuccessful.

EEG burst suppression was achieved with similar MAC multiples of sevoflurane and isoflurane: 2.14 MAC and 2.17 MAC, respectively. Both sevoflurane and isoflurane caused significant dose-dependent decreases in MAP, but CO was

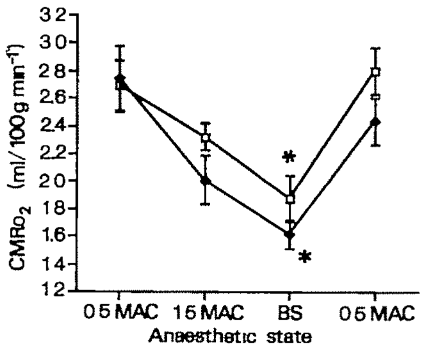

FIG. 1. Changes in $CMRo_2$ with sevoflurane (□) or isoflurane (◆). * Significant decrease within group compared with value obtained during the first exposure to 0.5 MAC. BS = End-tidal concentration of volatile anaesthetic associated with burst suppression pattern on the EEG.

not affected significantly (table I). Increasing concentrations of sevoflurane or isoflurane did not significantly alter CBF (table I). However, $CMRo_2$ decreased significantly during burst suppression compared with 0.5 MAC in both groups (fig. 1). There were no differences in cerebral or haemodynamic variables between the first and second exposures to 0.5 MAC. Two animals in the isoflurane group and one animal in the sevoflurane group required phenylephrine to maintain MAP > 60 mm Hg during the administration of the highest concentration of volatile anaesthetic.

DISCUSSION

The MAC values of enflurane and sevoflurane in this study are in agreement with those found in previous studies [6, 7]. The present study also demonstrates that, in contrast with enflurane, sevoflurane in concentrations up to 2.5 MAC caused neither EEG nor gross motor evidence of seizure activity in dogs that were rendered hypocapnic, exposed to intense auditory stimuli, or both. This property is important for any agent which might be used for patients in whom sustained seizure activity could lead either to an imbalance in the oxygen supply:demand ratio or to an increase in intracranial pressure. However, it must be emphasized that these results were obtained from dogs with normal brains and extrapolation to animals or patients with intracranial disease may be unwarranted. Similar results have been found in swine anaesthetized with desflurane, another new volatile ether anaesthetic [8], although desflurane is more highly fluorinated than enflurane—a property that might make it more epileptogenic [9]. However, the correlation of the degree of fluorination with epileptic potential is disputed [10]. Both desflurane (six fluoride atoms) and sevoflurane (seven fluoride atoms) are more highly fluorinated than enflurane (five fluoride atoms), and yet neither drug appears to cause seizure activity at clinically relevant doses during hypocapnia, in contrast with enflurane.

Sevoflurane and isoflurane had minimal effects on CBF, in agreement with an earlier study in rabbits [3]. However, in that study, isoflurane and sevoflurane were added to an existing nitrous oxide–morphine anaesthetic. We have shown previously that nitrous oxide increased CBF in rabbits anaesthetized with halothane or isoflurane and that the increases in CBF correlated positively with the initial end-tidal concentration of volatile anaesthetic [11]. By avoiding the use of nitrous oxide or other background anaesthetic agents in the present study, we may conclude confidently that sevoflurane and isoflurane affect CBF similarly in the dog at equipotent concentrations.

The changes in $CMRo_2$ observed during administration of sevoflurane in the present study are also in agreement with those in our previous study in the rabbit [3]. However, a study in pigs demonstrated that sevoflurane 1 MAC decreased cerebral cortical oxygen consumption by 50% compared with the awake state [12]. In the present study, we noted a 30% decrease in $CMRo_2$ in response to an increase in end-tidal concentration of sevoflurane from 0.5 MAC to 2.16 MAC. Neglecting a possible species difference, the pigs in the earlier study had an unusually high awake mean $CMRo_2$ (7.66 ml/100 g min^{-1}) compared with the value with sevoflurane 0.5 MAC (2.7 ml/100 g min^{-1}), suggesting that sevoflurane 0.5 MAC was associated with significant metabolic depression compared with the awake state.

Cucchiara, Theye and Michenfelder [13] studied the effects of isoflurane on CBF in dogs using the venous outflow model. They found that CBF increased in response to an increase in end-tidal concentration of isoflurane from 0.1% to either 1.4% or 2.4%, but found no difference in CBF between the two greater concentration . The results of the present study agree with their observations, although we studied slightly greater concentrations of isoflurane. In the present study, CBF did not change significantly in response to an increase in end-tidal concentration of isoflurane from 1.9% to 2.8%.

Inhalation induction of anaesthesia appeared more pleasant with sevoflurane than with either isoflurane or enflurane. In all cases, dogs readily inhaled sevoflurane and became unconscious quickly. In contrast, dogs breathing isoflurane or enflurane tended to struggle and breath-hold. Others have made this observation in dogs, swine and humans [7, 12, 14].

We conclude that the properties of isoflurane that make it suitable for use in neurosurgery, such as a negligible effect on CBF and a cerebral metabolic depressant effect, appear to be shared by sevoflurane. In contrast with enflurane sevoflurane did not appear to cause either EEG or gross motor evidence of seizure activity in hypocapnic dogs, even in the presence of auditory stimuli. In addition, inhalation induction of anaesthesia with sevoflurane appeared smoother than with either enflurane or isoflurane.

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REDISTRIBUTION OF CARDIAC OUTPUT CAUSED BY OPENING OF ARTERIOVENOUS ANASTOMOSES BY A COMBINATION OF AZAPERONE AND METOMIDATE

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SUMMARY

The effects of the butyrophenone, azaperone 5 mg kg^{-1} i.m. alone and after addition of the imidazole derivative metomidate 6 mg kg^{-1} i.v. were studied in eight conscious pigs. Fifteen minutes after administration of azaperone, systemic arterial pressure was reduced by 35% as a result of a 45% increase in systemic vascular conductance and 10% decrease in cardiac output ($\dot{Q}$). After azaperone, 23% of the radioactive labelled microspheres (15 (SD 1) μm) injected into the left atrium were detected in the lungs as a result of opening of arteriovenous anastomoses (baseline 3%). The increase in arteriovenous anastomotic blood flow was at the expense of the nutritional (= capillary) channels. Flow to the brain was maintained, but that to the left ventricle decreased in parallel with the reduction in arterial pressure. Vascular conductance of most other organs, except the skin, increased or was maintained. The addition of metomidate had no effect on $\dot{Q}$ because an increase in stroke volume (by 30%) compensated for the decrease in heart rate. Systemic vascular conductance decreased, most noticeably in the brain, left ventricle and skeletal muscle. We conclude that azaperone alone and in combination with metomidate had only a moderate effect on $\dot{Q}$, but caused a redistribution in favour of arteriovenous anastomoses.

KEY WORDS

Heart: cardiac output, circulatory effects Hypnotics: butyrophenones, azaperone, metomidate.

Butyrophenone compounds are used both in human (droperidol) and animal (azaperone) practice. Azaperone (4′-fluoro-4(2-pyridyl-1-piperazinyl)-butyrophenone) is used widely in pigs as a sedative when physical restraint or diagnostic procedures are required [1–4]. In addition, this drug is used frequently in combination with the veterinary analogue of etomidate, the imidazole derivative metomidate (methyl-1-(α-methylbenzyl)imidazol-5-carboxyl-hydrochloride), to provide anaesthesia for short-term surgical procedures in pigs [5]. In recent years several investigators have used this combination for both induction and maintenance of anaesthesia (with or without the addition of nitrous oxide) for physiological studies [6–8].

Although it has been demonstrated that the combination reduces systemic arterial pressure and cardiac output ($\dot{Q}$) [5, 9] detailed knowledge of regional cardiovascular responses is lacking. In the present study we investigated changes in central haemodynamics and regional blood flow (measured with radioactive microspheres) occurring in conscious pigs after sedation with azaperone and additional administration of metomidate. It is known that, in anaesthetized, but not conscious, animals a large fraction of the microspheres is trapped in the lungs because of shunting by arteriovenous anastomoses [7,

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10–13]. We therefore paid special attention to the occurrence of this phenomenon.

MATERIALS AND METHODS

After an overnight fast, cross-bred Landrace × Yorkshire pigs (20–25 kg, $n = 8$) pretreated with a mixture of procaine penicillin-G 300000 u. i.m. and benzathine-penicillin-G 300000 u. i.m. (Duplocillin, Gist-Brocades N.V., Delft, The Netherlands) were anaesthetized with ketamine 30 mg kg^{-1} i.m. (Aescoket, Aesculaap B.V., Boxtel, The Netherlands) [3]. The trachea was intubated and the lungs ventilated with a mixture of 66% nitrous oxide and 1% halothane in oxygen. A jugular vein and common carotid artery were cannulated for administration of drugs and measurement of systemic arterial pressure, acid–base state and blood-gas tensions (ABL-3 and OSM_2, Radiometer, Copenhagen, Denmark).

The chest was opened through the left fifth intercostal space to expose the heart. The left atrium was cannulated for injection of radioactive microspheres (15 (SD 1) μm diameter), labelled with cerium-141, ruthenium-103 or niobium-95 (NEN Chemicals GmbH, Dreieich, West Germany) and suspended in saline containing one drop of Tween 80. Via the third intercostal space, an electromagnetic flowprobe (Skalar, Delft, The Netherlands) was positioned around the ascending aorta. $\dot{Q}$ was calculated by adding myocardial blood flow (determined with radioactive microspheres) to the electromagnetic flow readings. Catheters and wires were tunnelled subcutaneously to the back, the chest was closed and the animals allowed to recover. After operation, the animals received bolus injections of amoxicillin 500 mg i.v. daily (Clamoxil, Beecham Farma B.V., Amstelveen, The Netherlands) and, during the first week, kanamycin 500 mg (Kamynex, Gist-Brocades N.V., Delft, The Netherlands) to prevent infection. The catheters were flushed daily with an isotonic saline solution containing heparin 500 iu ml^{-1}. After 1 week of post-surgical recovery, at least eight to 10 sessions were held to adapt the animals to the laboratory facilities and experimental conditions; when animals are adapted to experimental conditions, systemic haemodynamic parameters and regional blood flows change less than 5% over 1 h [14, and unpublished data from our laboratory]. The experimental study was performed 3–4 weeks after instrumentation. Antibiotics were withheld at least 24 h before the experiment. Neuromuscular blocking agents were not administered.

Experimental procedure

After baseline systemic haemodynamic and arterial blood-gas data had been recorded, $1–2 \times 10^6$ microspheres were injected i.v. while an arterial reference sample was withdrawn (10 ml min^{-1}) for calibration of regional blood flow measurements [10]. Subsequently, the animals received azaperone 5 mg kg^{-1} i.m. and 15 min later, after all measurements had been repeated, metomidate 6 mg kg^{-1} i.v. was administered. Immediately thereafter, the trachea was intubated and the lungs ventilated with 66% nitrogen in oxygen to maintain arterial blood-gas values at baseline. The last set of values was obtained 10 min after i.v. injection of metomidate, while the animals were in a stable haemodynamic condition.

At the end of each experiment the animal was killed with an overdose of pentobarbitone sodium. Tissue was dissected, weighed and placed in vials. The brain was divided into left and right cerebral hemispheres, diencephalon, brain stem and cerebellum. The heart was stored in 10% formaldehyde for 48 h and subsequently the left ventricle was dissected into three layers of equal thickness. The radioactivity in the vials was counted for 10 min in a gamma-scintillation counter (Packard Minaxi Autogamma 5000) with a multichannel pulse height analyser using suitable windows for discrimination of the different isotopes. The amount of blood distributed to the various tissues ($\dot{Q}$tis) was calculated as:

$$\dot{Q}\text{tis (ml min}^{-1}) = (I\text{tis}/I\text{art}) \times \dot{Q}\text{art}$$

Where Itis and Iart are, respectively, the radioactivity (c.p.m.) in a particular tissue and that of the arterial blood sample, while $\dot{Q}$art is the rate of withdrawal of the blood sample. Vascular conductances were calculated by dividing blood flow by mean arterial pressure.

Statistical analysis and data presentation

Statistical analysis was performed using the Duncan New Multiple Range test after parametric two-way analysis had revealed that the samples represented different populations. Statistical significance was accepted at $P < 0.05$. All values are presented as mean (SEM).

RESULTS

Arterial acid–base and blood-gas state

Arterial blood-gas values did not change from respective baseline values (pH 7.46 (0.03); Pa_{CO_2} 4.9(0.1)kPa; Pa_{O_2} 10.1(0.5) kPa; oxygen saturation 95 (1)%; haemoglobin 5.0 (0.2) mmol litre^{-1}), either during spontaneous ventilation after azaperone or during controlled mechanical ventilation after metomidate.

Systemic haemodynamics

Administration of azaperone decreased $\dot{Q}$ by 10% and mean arterial pressure (MAP) by 35% (fig. 1). Because the decrease in MAP considerably exceeded the decrease in $\dot{Q}$, calculated systemic vascular conductance increased by 45%. The decrease in $\dot{Q}$ was secondary to a reduction in stroke volume by 13% as heart rate remained unaffected. After the i.v. administration of metomidate, $\dot{Q}$ was maintained, as the increase in stroke volume of 30% counterbalanced the drug-induced bradycardia. In view of the slight increase in arterial pressure and unchanged cardiac output, systemic vascular conductance was attenuated.

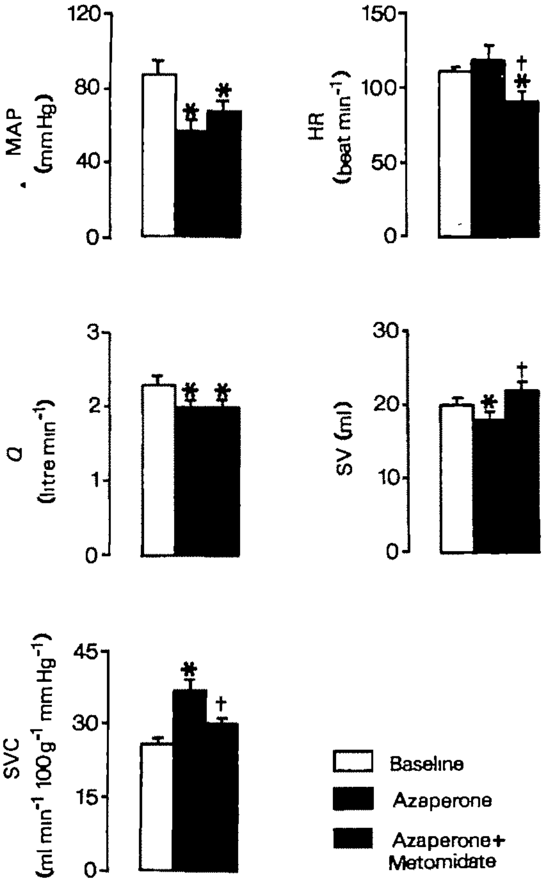

FIG. 1. Effects of azaperone 5 mg kg^{-1} i.m. alone and after addition of metomidate 6 mg kg^{-1} i.v. on systemic haemodynamics in eight pigs (mean (SEM)). MAP = Mean arterial pressure; HR = heart rate; $\dot{Q}$ = cardiac output; SV = stroke volume; SVC = systemic vascular conductance $^*P < 0.05$ *vs* baseline; $†P < 0.05$ *vs* azaperone.

Distribution of cardiac output to arteriovenous anastomotic and nutritional channels

During baseline conditions only 3% of the microspheres were trapped by the lungs (mainly bronchial arterial blood flow [15]). After administration of azaperone, blood flow was redistributed in favour of arteriovenous anastomoses, as 23% of the microspheres were trapped in the lungs, while the nutritional capillary blood flow decreased in parallel with arterial pressure (fig. 2). Consequently the vascular conductance of the nutritional vasculature was not affected. After administration of metomidate there were no significant changes in nutritional and arteriovenous blood flows. Arteriovenous conductance was not affected, but nutritional vascular conductance decreased and was responsible, therefore, for the attenuation of systemic vascular conductance.

Distribution of nutritional blood flow

Azaperone decreased left ventricular myocardial blood flow (fig. 3), which was distributed

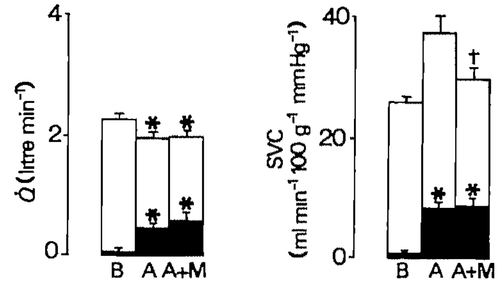

FIG. 2. Effects of azaperone 5 mg kg^{-1} i.m. alone (A) and after addition of metomidate 6 mg kg^{-1} i.v. (A+M) on the contribution of the arteriovenous anastomoses (■) and the nutritional vascular bed (□) to cardiac output ($\dot{Q}$) and systemic vascular conductance (SVC). The contribution of the nutritional vessels has been superimposed on that of the arteriovenous anastomoses such that the sum reflects $\dot{Q}$ and SVC. The symbols for statistically significant changes and the SEM bars are those for the two fractions $^*P < 0.05$ *vs* baseline (B); $†P < 0.05$ *vs* azaperone (A).

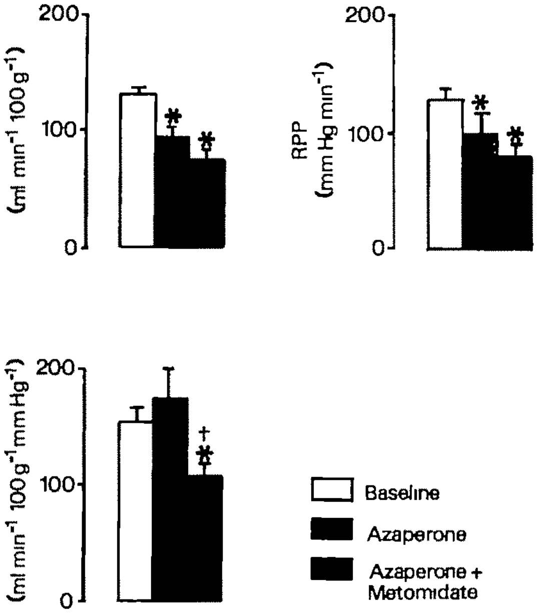

FIG. 3. Effect of azaperone 5 mg kg^{-1} i.m. alone and after addition of metomidate 6 mg kg^{-1} i.v. on transmural left ventricular blood flow (LVBF), left ventricular oxygen demand estimated by the rate-pressure product (RPP) and left ventricular vascular conductance (LVVC) (mean (SEM)). $^*P < 0.05$ *vs* baseline; $^†P < 0.05$ *vs* azaperone.

homogeneously over the myocardial layers, as the endocardial : epicardial ratio did not change from its baseline value (1.39 (0.05); not shown). A 27 % decrease in transmural blood flow accompanied a 22 % decrease in oxygen demand (estimated by the rate–pressure product). As the decrease in left ventricular blood flow was of a magnitude similar to the decrease in mean arterial pressure, there was no change in left ventricular vascular conductance. Addition of metomidate decreased further left ventricular blood flow but, as the oxygen demand changed similarly, there was no detrimental effect on myocardial oxygen supply : demand ratio. Whereas there was no change in left ventricular conductance with azaperone, there was a marked decrease in conductance after metomidate was added.

In the conscious animals, the brain stem received 30–35 % less blood than other parts of the brain (table I). Azaperone caused marked vasodilatation, as blood flows to all cerebral regions were maintained despite the 35 % decrease in arterial pressure. However, after addition of metomidate, blood flows to all parts were reduced by 40–55 %, despite the slight increase in arterial pressure. From the changes in arterial pressure and flow it follows that the conductance of all regions of the brain decreased to 60–80 % of baseline values.

Following azaperone, blood flow to some organs was maintained (liver, spleen, right ventricle and skeletal muscle) or even increased (adrenals). Blood flow to the kidneys, stomach, small intestine and skin were reduced (table II). Vascular conductance was diminished in the skin, did not change in kidneys and skeletal muscle, stomach and small intestine, and increased in liver, spleen and adrenals. The addition of metomidate had no effect on blood flow to some organs (liver, spleen, small intestine, stomach and kidneys), but largely abolished the azaperone-induced increase in blood flow to the adrenals, while it reduced flow to the

TABLE I. *Regional cerebral haemodynamics after azaperone 5 mg kg^{-1} i.m. and addition of metomidate 6 mg kg^{-1} i.m. in eight pigs (mean (SEM)).* $^*P < 0.05$ vs *baseline*; $^†P < 0.05$ vs *azaperone*; $^§P < 0.05$ vs *all other brain regions*

	Baseline	Azaperone	Azaperone + metomidate
Blood flows (ml min^{-1} 100 g^{-1})			
Right hemisphere	77 (5)	79 (6)	35 (3)*†
Left hemisphere	76 (6)	76 (4)	36 (2)*†
Diencephalon	77 (7)	81 (9)	38 (2)*†
Cerebellum	81 (5)	80 (5)	49 (3)*†§
Brain stem	53 (5)§	56 (3)§	33 (3)*†
Total brain	74 (4)	74 (4)	35 (3)*†
Conductances (10^{-2} ml min^{-1} 100 g^{-1} mm Hg^{-1})			
Right hemisphere	90 (9)	154 (29)*	53 (5)*†
Left hemisphere	92 (6)	146 (14)*	54 (3)*†
Diencephalon	95 (7)	158 (23)*	57 (6)*†
Cerebellum	100 (5)	162 (27)*	73 (7)†§
Brain stem	65 (5)§	113 (18)*§	51 (7)†
Total brain	86 (7)	141 (20)*	54 (5)*†

TABLE II. *Regional haemodynamics after azaperone 5 mg kg^{-1} i.m. and addition of metomidate 6 mg kg^{-1} i.m. in eight pigs (mean (SEM)).* *$P < 0.05$ *vs baseline*; †$P < 0.05$ *vs azaperone*

	Baseline	Azaperone	Azaperone + metomidate
Blood flows (ml min^{-1} 100 g^{-1})			
Liver	19 (4)	18 (3)	14 (3)
Spleen	160 (10)	144 (17)	123 (18)
Kidneys	366 (36)	244 (40)*	252 (34)*
Adrenals	127 (5)	276 (40)*	191 (27)*†
Stomach	42 (11)	19 (5)*	21 (5)*
Small intestine	50 (6)	32 (4)*	36 (6)*
Right ventricle	88 (5)	80 (13)	51 (6)*†
Skeletal muscle (iliopsoas)	13.6 (4.7)	8.3 (2.6)	3.2 (0.3)*
Skin	6.8 (1.0)	2.0 (0.3)*	1.1 (0.3)*
Conductances (10^{-2} ml min^{-1} 100 g^{-1} mm Hg^{-1})			
Liver	22 (5)	37 (11)*	22 (5)†
Spleen	185 (14)	261 (28)*	179 (20)†
Kidneys	424 (48)	434 (63)	366 (36)
Adrenals	146 (9)	494 (58)*	301 (57)*†
Stomach	51 (14)	36 (10)	29 (6)*
Small intestine	59 (8)	65 (14)	52 (7)
Right ventricle	102 (9)	143 (20)*	77 (9)†
Skeletal muscle (iliopsoas)	15.3 (4.8)	15.3 (4.5)	4.9 (0.4)*†
Skin	7.6 (0.8)	3.6 (0.6)*	1.7 (0.3)*†

right ventricle, skeletal muscle and skin. Consequently, metomidate abolished (adrenals) or attenuated (liver, spleen, right ventricle) the azaperone-induced vasodilatation in some organs, while in others the reduction in vascular conductance was enhanced (skin) or became apparent (stomach, skeletal muscle).

DISCUSSION

Azaperone

Azaperone-induced hypotension has been reported by others [4, 5, 16]. Lees and Serrano [16] also found that this was caused by systemic vasodilatation rather than a decrease in $\dot{Q}$. Although $\dot{Q}$ was affected only minimally, there was profound redistribution of blood flow, implying an opening of arteriovenous anastomoses [7, 10–13]. In the pig, these anastomoses are abundantly present in the skin [7] and play a major role in the regulation of body temperature. The opening of these anastomoses by azaperone may, therefore, explain the decrease in body temperature described by others [1, 2]. The increase in conductance of the arteriovenous anastomoses was responsible also for the increase in systemic vascular conductance, as the changes in conductance of the nutritional vessels counterbalanced each other. These results suggest that the mechanism responsible for opening of the arteriovenous anastomoses is the same as the mechanism for the hypotensive action. However, both the mechanisms for opening of the arteriovenous anastomoses in general and that by which azaperone decreases arterial pressure are largely unknown. It has been suggested that azaperone possesses α-adrenoceptor antagonistic activities [17–19]. As the physiological regulation of arteriovenous anastomotic blood flow is mediated in part by the sympathetic nervous system [20], it may be amenable to α-adrenoceptor antagonism. However, other mechanisms such as active neurogenic vasodilatation, for which no neurotransmitter has yet been identified [18], may be involved in the control of arteriovenous anastomotic blood flow. Also, as with noradrenaline, the arteriovenous anastomoses are constricted by 5-hydroxytryptamine [21]. In addition, butyrophenones possess antidopaminergic properties and dopamine is believed to play a role in central regulation of body temperature [22], so that the opening of arteriovenous anastomoses by azaperone could conceivably be caused by a mechanism not related to α-adrenoceptor antagonism. The clinical analogue of azaperone, the butyrophenone droperidol, induces hypotension in man by systemic vasodilatation, which is probably secondary to the combination of central nervous effects and block of vascular α-adrenoceptors [23]. The opening of arteriovenous anastomoses could also be involved, but this may be difficult to assess in man.

Left ventricular blood flow decreased in accord with the reduction in myocardial oxygen demand. As the reduced arterial pressure was responsible for the reduced oxygen demand, left ventricular blood flow was reduced without affecting coronary vascular conductance. On the other hand, cerebral flow was well maintained in spite of the hypotensive action of azaperone. Consequently, there was a marked increase in the vascular conductance of all regions of the brain. From the present studies, it cannot be concluded whether cerebral vasodilatation was caused by a metabolic regulation or by a direct action of the drug.

Azaperone and metomidate

In the present study, the addition of metomidate attenuated the azaperone-induced decrease in arterial pressure, by decreasing the systemic vascular conductance. From figure 2 it is clear that the decrease in vascular conductance was restricted to the nutritional channels, as conductance of the arteriovenous anastomoses remained unchanged. The decreases in vascular conductance were most noticeable in the brain, left ventricle and skeletal muscle. In the brain this was probably secondary to a decrease in cerebral metabolism similar to that shown for its clinical analogue etomidate [24, 25]. From the present study we cannot conclude if cerebral metabolism decreased. In order to measure oxygen consumption, knowledge of the oxygen content of cerebral venous blood is necessary, but this cannot be readily obtained. Sampling from the internal jugular vein does not provide reliable information because in pigs it does not selectively drain blood from the cerebral circulation [26].

The addition of metomidate caused further reduction in left ventricular oxygen demand. In contrast with azaperone, this occurred by decrease in heart rate rather than decrease in arterial pressure. The reduced metabolic needs were accompanied by vasoconstriction, as arterial perfusion pressure was not significantly affected. These results are in agreement with those reported for etomidate in animals [24] and in man [25, 27].

Lees and Serrano [16] have shown that the actions of azaperone in ponies persist for at least 40–60 min. Our observations with metomidate were made within 30 min of administration of azaperone. Nevertheless, it could be argued that, because of differences in kinetics, our observations in pigs could be explained by washout of azaperone. However, the nature of the changes does not support such a hypothesis.

Clinical implications

Azaperone is used widely in veterinary practice, alone or in combination with metomidate. It has been claimed to have minor effects on cardiovascular function, despite reports of its hypotensive action [2, 3]. In view of our findings, such a claim is not warranted. Furthermore, although cardiac output was well maintained, large changes occurred in distribution. Opening of arteriovenous anastomoses shown in the present study and the earlier reports on severe hypothermia [1], suggest that the drug interferes with thermoregulation and that care must be taken to maintain body temperature, both in veterinary practice and in physiological preparations. To our knowledge, no reports on effects of droperidol on body temperature of man are available.

Azaperone and metomidate are not used in human practice, but their clinical analogues, droperidol and etomidate, respectively, have been shown to exert similar central haemodynamic actions [28]. This may also be true for regional blood flow.

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FAILED TRACHEAL INTUBATION

T. A. KING AND A. P. ADAMS

The incidence of failed intubation is higher in obstetric than other surgical patients. Samsoon and Young described incidences of 1:280 and 1:2230, respectively [97]. Reviewing 6 years' experience in a teaching maternity unit, Lyons reported an incidence of approximately 1:300 [66] which serves to alert us to the high risk present in the obstetric population. More important is the incidence of adverse outcome from failed intubation as this reflects deficiencies in management and acts as a yardstick for improvement. In the series of obstetric cases reported by Lyons there was a safe outcome for mother and baby in the nine patients in whom intubation had failed [66]; however, the number of failed intubations considered was small. Other audits quote morbidity and mortality figures without relation to the total number of cases of failed intubation. Among 58 deaths totally attributable to anaesthesia, Lunn and Mushin found four related to problems with tracheal intubation [65]. In the more recent Confidential Enquiry into Perioperative Deaths (1987), one of the three deaths related solely to anaesthesia was ascribed to failed intubation [22]. Both these audits specifically excluded obstetric anaesthesia. Marx and her colleagues performed a computer analysis of deaths after operation. Considering the course of nearly 30000 general anaesthetics for non-obstetric surgical patients, there were two deaths from failed intubation. However, the total number of intubations and the number of successfully managed failed intubations were not given [71]. Pedersen and Johansen found no serious morbidity attributable to anaesthesia from failed intubation in a review of 6252 general anaesthetics; exclusion of obstetric anaesthesia was not mentioned [89]. In the *Reports on Confidential Enquiries into Maternal Deaths in England and Wales 1973–1984*, approximately 41% of deaths directly ascribable to anaesthesia were caused by difficulties with tracheal intubation [35–38].

Audit of serious anaesthetic complications related to intubation may be found in medico–legal records. Over a 10-year period, 102 anaesthetic mishaps leading to death or serious neurological damage were reported to the Medical Protection Society. Of these, 15 (14.8%) were caused primarily by problems at intubation. Failed intubation was the second commonest cause of mortality or serious morbidity during anaesthesia [43]. During a 13-year period of reports to the Medical Defence Union, there were 326 cases of death and cerebral damage thought to be the result of errors in anaesthetic technique. Errors associated with tracheal intubation accounted for 31%, this being the most important group [110]. It has been estimated that, in the developed world alone, 600 deaths occur annually from complications at the time of tracheal intubation [7]. Continuing audits of incidence of failed intubation and adverse outcome are required, with evaluation of the circumstances under which they occur.

ANATOMICAL FACTORS IN FAILED INTUBATION

It is the unexpected difficult intubation that leads to disaster [6]. Predicting a problem at intubation should not be difficult where there is obvious pathology involving the neck, maxillo–facial, pharyngeal and laryngeal structures, whether or not this is associated with specific medical conditions or congenital syndromes. However, several patients of apparently normal appearance unexpectedly present great difficulties at intubation [97]. A study of anatomical factors in these

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patients should improve ability to predict and manage a potential failed intubation.

The importance must be stressed of correct positioning of the head and neck during direct laryngoscopy in order to achieve alignment of the axes of the mouth, pharynx and larynx to permit tracheal intubation [6, 7]. The position of flexion of the lower portion of the cervical spine combined with extension of the head at the atlanto–occipital joint has been well described and illustrated by Murrin [79]. Horton and his colleagues have defined a standard intubating position for research and teaching purposes: the lower neck flexion is 35° and extension of the plane of the face 15°, each angle measured relative to the horizontal plane [49]. Inability to extend the head at the atlanto–occipital joint is an important cause of difficult intubation [7, 81, 119]. The amount of extension that can be achieved at this joint is limited by the abutment of the occiput against the posterior tubercle of the atlas. The greater the atlanto–occipital distance in the neutral position, the greater the degree of extension that is possible. When the posterior tubercle of the atlas is already in contact with the occiput in the neutral position, attempts to extend the head result in anterior bowing of the cervical spine, and forward displacement of the larynx. Consequently, laryngoscopy is difficult [81].

The atlanto–occipital gap may be assessed by examining the lateral radiograph of the cervical spine in the neutral position, the measurement being made from the occiput to the spine of the atlas. Numerous reports have confirmed the value of this radiographic assessment in predicting a difficult intubation [7, 81, 117, 120]. There is wide variation in the atlanto–occipital distance, but at one extreme the occiput appears to be in contact with the atlas in the neutral position. Of greater importance is clinical assessment of extension at the atlanto–occipital joint. Nichol and Zuck [81] stressed the importance of raising the occiput above the shoulders before testing for head extension: this manoeuvre helps to eliminate error in assessment from anterior bowing of the cervical spine. Although limitation in head extension may occur secondary to pathological conditions such as rheumatoid arthritis, it may also occur secondary to anatomical variations of the atlanto–occipital gap in people who are otherwise regarded as normal [81]. Unexpected failure of intubation is likely to occur in this group of patients.

Recent work has demonstrated that, in healthy volunteers undergoing laryngoscopy, a mean extension of 25° occurs at C1–2, and to consider movement between C0–1 and C1–2 as separate may be inappropriate [50]. Despite correct positioning of the head and neck, other anatomical factors may interfere with the line of vision from mouth to vocal cords. Cormack and Lehane have categorized these as forward displacement of the larynx or upper teeth, or backward displacement of the tongue, with head extension and mouth opening being contributing factors [32]. These categories are discussed below.

Westhorpe has studied the position of the larynx in children and its relationship to the ease of intubation [116]. There is a marked descent of the larynx relative to the cervical spine during the first 2 years of life. The position then remains fairly static until puberty, when further descent of laryngeal structures occurs. When the larynx has a high position, as in children younger than 2 years, no advantage in visualization of the larynx is obtained from flexion of the neck during oral intubation because there are no intervertebral joints above the level of the larynx. A more effective procedure is to apply external pressure to the larynx, thus increasing the intubation angle and improving the view [116]. Similarly, a high anterior larynx in an adult may be brought into view by external laryngeal manipulation. Zuck has suggested that anterior convexity of the cervical spine determines the position of the larynx in relation to the coronal plane. Marked anterior convexity of the cervical spine is associated with an anteriorly positioned larynx. Furthermore, if there is marked convexity of the cervical spine, there is no atlanto–occipital gap [121].

Three factors should be considered when assessing the upper teeth as a cause of difficult intubation. These include effective maxillary length and height, and the state of the dentition. Several studies have failed to identify maxillary height or length as a factor [7, 111, 117] although Cass, James and Lines cited relative overgrowth of the premaxilla resulting in protruding upper incisors [26]. These observations were based on case reports alone, whereas other studies were case controlled. Wilson and his colleagues [119] found "buck teeth" to be a risk factor in predicting difficult intubation and this has been supported by the observations of other investigators [26, 120]. White and Kander did not find protruding upper teeth to be a particularly important factor [117]. The part played by dental configuration is supported by observations that edentulous patients do not usually present an intubation problem [120], although this is not always the case [7].

Mandibular configuration, tongue mass and mobility of these structures are important determinants of laryngeal visibility. A receding mandible has been associated with difficult intubation [7, 26, 119]. White and Kander found the most important factor which determined the ease of laryngoscopy was the posterior depth of the mandible. An increase in this measurement was thought to hinder displacement of the soft tissues by the laryngoscope blade. The posterior depth of the mandible was expressed as a ratio of the effective mandibular length to relate it to the general size of the skeleton. It was suggested that, if the effective mandibular length is less than 3.6 times the posterior depth of the mandible, direct laryngoscopy is difficult and *vice versa* [117]; these observations were supported by Zuck [120]. Others have found an increased anterior depth of the mandible in patients who present difficulty in intubation, necessitating wider opening of the mouth during direct laryngoscopy [26, 117]. However, not all studies have confirmed the significance of posterior and anterior depth of the mandible [7, 111, 119]. Using radiological techniques, Bellhouse and Doré found that the ratio of the mandibular space to the total length of the tongue is a good predictor of difficult intubation [7], thus introducing the important concept that bony structures should be considered in conjunction with the soft tissues with which they are closely associated. It has been suggested that a long, high-arched palate associated with a long mouth causes difficult intubation by reducing the space between the posterior angles of the mandible [26]. Case controlled studies have not confirmed this observation, although the abnormality may not be sufficiently common to establish its significance [7, 111, 117]. Mallampati and his colleagues [70] and subsequently Samsoon and Young [97] described a clinical test relating tongue size to ease of laryngoscopy. It is based on the hypothesis that when the base of the tongue is disproportionately large, the tongue overshadows the larynx, resulting in poor or difficult exposure of the latter during direct laryngoscopy. Similarly, a disproportionately large tongue masks visibility of the faucial pillars, uvula and soft palate. Assessment is made with the patient sitting upright with the head in the neutral position, the mouth open as wide as possible and the tongue protruded to a maximum. The observer sits opposite the patient at eye level to inspect the pharyngeal structures. When the uvula and the soft palate cannot be seen because of obstruction by the base of the tongue, laryngoscopy is likely to be difficult [70, 97].

Limited movement of the mandible is a recognized cause of difficult intubation [26, 79, 117]. This may be related to temporo–mandibular joint dysfunction or trismus but, in addition, a relatively large mandible and a short thick neck, or a mandible with short descending rami may contribute to the problem [26]. Classic teaching is to assess the interdental gap. However, Wilson and his colleagues found two aspects of jaw movement were significant when assessing risk factors for difficult intubation. These were interdental gap and subluxation of the jaw (maximal forward protrusion of the lower incisors beyond the upper incisors) [119]. While mouth opening permits adequate insertion of the laryngoscope, good forward luxation of the mandible also provides additional space for forward displacement of the tongue.

Patil, Stehling and Zauder have used the thyro–mental distance (distance from the thyroid notch to the mental prominence when the neck is extended fully) to anticipate difficulty with intubation [87]. The normal measurement is 6.5 cm or greater. If the distance is 6.0–6.5 cm without other anatomical problems, laryngoscopy and intubation are difficult, but usually possible. A distance of less than 6 cm suggests that laryngoscopy may be impossible [87]. Other reports have confirmed the value of this measurement in predicting difficult intubation [72]. This single measurement is likely to be influenced by several anatomical factors, including head extension, position of the larynx, and depth and length of the mandible. Classically, it is taught that a short muscular neck causes difficult intubation [26, 79] because of interference with mobility of the mandible [26], but increased tongue mass, reduced head extension and a high anterior larynx also are important factors. In addition, obesity has been identified as a risk factor [119].

Horton and his colleagues have studied the mechanism of laryngoscopy. When the tip of the curved Macintosh laryngoscope blade is introduced at the angle between the base of the tongue and the epiglottis, the optimal position should be immediately behind or below the body of the hyoid bone. The principal mechanism of elevation of the epiglottis is related to forward traction on the hyoid by the blade tip. During laryngoscopy the hyoid is moved forward and downward. Failure to control the hyoid is cited as a common mechanism in difficult intubation using the Macintosh blade. In eight patients who presented difficulty in intubation, failure to place the tip of the blade near the hyoid, or partial calcification of the stylohyoid ligaments, hindered forward movement of the hyoid [47, 48, 50]. Using the technique of magnetic resonance imaging, it has been established that when the angle between the epiglottis and the base of the tongue reaches 90°, intubation becomes difficult [14]. This "floppy" epiglottis can be elevated directly by a straight-bladed laryngoscope. Nevertheless, when using this blade difficulty may be encountered when negotiating tight oropharyngeal corners, because the blade may impact against the upper teeth and possibly against a cervical vertebra [7].

The pregnant patient

Why should the incidence of failed intubation be almost eight times higher in obstetric patients than in other groups? Part of the reason may be that anaesthetists adopt a failed intubation drill much earlier in this group—with good reason [67]—but what of anatomical considerations? As bony structures remain unchanged, the problem must reside with the soft tissues and their mobility, with perhaps secondary effects on the mobility of bony structures. Is there any evidence for this? During pregnancy, capillary engorgement takes place so that the mucosa of the nasopharynx and larynx becomes swollen and reddened. These changes simulate inflammation and may cause voice changes and make nasal breathing difficult for some women at term [12]. In addition, total body water increases during pregnancy. Generalized oedema may occur in women who are normotensive and whose pregnancies are unremarkable in every other respect. The oedema of pregnancy appears to be caused by the effect of oestrogens on the ground substance of connective tissue, although it is not obvious clinically in all pregnant women. Deposition of fat also takes place [53]. If tongue size and mobility are important, there are physiological reasons why these could change during pregnancy.

Boliston has suggested that immobility of the floor of the mouth is a common problem [11]. Perhaps this is caused by both tongue enlargement and increased tissue engorgement making elevation of the hyoid difficult during laryngoscopy. Laryngeal oedema associated with pre-eclampsia is well documented as a cause of difficult intubation [21, 56]. However, it has also been recorded in patients without pre-eclampsia in whom strenuous efforts associated with labour result in increased venous pressure in the head and neck. This leads to interstitial oedema of the laryngeal structures. Failed or difficult intubation has been recorded under these circumstances [56, 68]. Other factors believed relevant in the difficult obstetric intubation include full dentition, thoracic lift from a badly placed wedge interfering with a good intubating position, and over-enthusiastic cricoid pressure distorting the position of the larynx [66]. If a patient with large breasts is placed in the supine and laterally tilted position, insertion of the laryngoscope blade may be difficult because there is little room between the breasts and the mouth for the handle of a conventional laryngoscope [57].

Assessment of anatomical factors

A knowledge of detailed anatomical factors is essential if difficult intubation is to be predicted. Bony structures, soft tissues and their mobility should be examined. The contribution of the soft tissues in a difficult intubation has been underestimated. This is especially so with the mobility of the base of the tongue [11, 29, 48]. No single anatomical factor determines the ease of direct laryngoscopy and therefore, with the exception of patients with obvious pathology, no single anatomical factor can be used to predict a difficult intubation [7, 111, 119]. A careful history and clinical examination should elicit the obvious problems. In addition, several more specific assessments have been described. These include oropharyngeal inspection, head and neck movement (with particular attention to the atlanto-occipital joint), jaw movement (both interdental gap and maximal forward protrusion of the lower incisors beyond the upper incisors), thyromental distance, examination for evidence of a receding mandible and buck teeth, and an assessment of body weight [7, 70, 72, 81, 87, 97, 119]. These examinations are quick, simple and may be performed at the bedside. With present knowledge there is little excuse for not attempting a preoperative assessment of the relevant anatomical factors such that it becomes second nature. The appropriate skills and equipment may be mobilized when necessary for a predicted difficult intubation [7]. Undoubtedly, some patients may be predicted falsely to present difficulty, and this may have implications if expertise and equipment are frequently and unnecessarily mobilized. Other patients are at risk where the problem remains unidentified, so that it is essential that anaesthetists have appropriate training to manage patients in whom intubation proves impossible [119].

AETIOLOGY OF MORBIDITY AND MORTALITY ASSOCIATED WITH FAILED INTUBATION

"Although intubation problems will occur from time to time during anaesthesia and failure to intubate successfully may be unavoidable, it is seldom possible to defend any case where a patient dies or suffers brain damage as a direct result of unsuccessful tracheal intubation" [43]. Bearing in mind that failure to intubate may be unavoidable in certain circumstances, it is worth reviewing the factors which may contribute to a disastrous outcome.

Preoperative assessment

It is taken for granted that preoperative assessment of patients is essential [22]. Improved and worthwhile methods of predicting difficult intubation exist, those patients with a full stomach being especially at risk [8]. Failure to assess these risks, so that appropriate precautions are not taken, contributes to serious morbidity or mortality.

Experience of the anaesthetist

The judgement and skill of the physician is of paramount importance in preventing anaesthetic deaths as a result of failed intubation [71]. This has been borne out clearly in the *Confidential Enquiries into Maternal Deaths in England and Wales*, in which avoidable deaths at intubation have been attributed to lack of training and experience. Trainees require direct supervision until they have learned acceptable methods of management when intubation is difficult. Responsibility lies with both junior and consultant staff. A death was reported after a junior anaesthetist attempted to manage a high risk case single-handed without communicating with his consultant. Similarly, a death occurred where difficulty had been anticipated and discussed with senior staff, but anaesthesia and surgery were delegated to junior staff [35, 37, 38].

Cormack and Lehane have pointed out that difficult intubation is a fairly rare situation and it may be difficult for staff in training to gain the necessary experience [32]. They may, therefore, be unprepared for this situation when it does occur, and some may not have met the problem before starting obstetric anaesthesia. A technique for training is described whereby a grade 3 intubation (only epiglottis seen) is simulated during any routine operating list, the trainee then learning to intubate using an appropriate technique [32]. Others have supported this approach [75, 119].

Trained assistants

Lack of skilled and dedicated assistance may be identified as contributing to morbidity and mortality following failed intubation [35–38]. The role of such assistants (Anaesthetic Nurses or Operating Department Assistants in the U.K.) is vital in assisting the anaesthetist to achieve a smooth induction and intubation, and to provide expert help should a crisis occur.

Persistent attempts at intubation

Determination that a tracheal tube must be passed at all costs, with persistent attempts at intubation and sometimes repeated doses of suxamethonium, is to be condemned. The complications of hypoxia and aspiration increase as such attempts become prolonged. It is tempting for a more senior anaesthetist arriving on the scene to continue with efforts to intubate, yet this too has been a characteristic of some fatalities [35–38, 43, 110]. For obstetric anaesthesia Cormack and Lehane suggest no more than three attempts should be made in the case of a grade 3 difficult intubation before starting a failed intubation routine, and that with a grade 4 (not even epiglottis exposed) the failed intubation routine should be started without delay [32]. Lyons, also discussing obstetric anaesthesia, comments that where the trachea cannot be intubated, ventilation with a facemask and airway may also be difficult. Accordingly, trainees are taught that repeat doses of suxamethonium should not be administered unless it is certain that intubation can be accomplished [66]. It seems reasonable to extend these principles to non-obstetric patients, especially those in whom there is a risk of aspiration or in whom maintenance of the airway is compromised.

Oesophageal intubation

Undiagnosed oesophageal intubation is lethal. This accounted for 46% of the 41 deaths related to tracheal intubation in the *Confidential Enquiries into Maternal Deaths in England and Wales 1973–1984* [35–38]. Medico–legal audits support this as being the commonest error of intubation leading to serious neurological damage or death [43, 110]. Preoxygenation may delay both the onset of cyanosis and the change in cardiovascular signs and therefore delay recognition that the tube is not in the trachea [37, 90, 113]. Inadvertent oesophageal intubation must always be considered as a cause of hypoxaemia, even when 20 min has elapsed after intubation. The start of surgery adds to the potential for disaster because of added distractions at that time [113]. Clinical signs for distinguishing between oesophageal and tracheal intubation may be misleading including, for example, movement and feel of the reservoir bag of the breathing system, chest movement and auscultation, evidence of gastric distension and detection of airflow with chest compression [43, 52, 90, 110]. Reliance on these signs has resulted in disaster [43, 90]. To be certain that the tracheal tube is in the trachea, it is necessary to observe that the arytenoid cartilages lie posterior to the tube [110]. Confirming the position of the tube using direct laryngoscopy following a difficult intubation may not be easy, although a simple technique has been described to facilitate this manoeuvre. With the laryngoscope blade still in the mouth after oral tracheal intubation, posterior displacement of the tube towards the palate assists in bringing the tube and vocal cords into view [41]. Visualization of the tracheal rings and the carina with a fibreoptic endoscope verifies correct placement of the tracheal tube [10].

Capnography provides a rapid and reliable guide for tracheal tube placement [44, 54, 62, 78]. However, ventilation using a facemask before intubation can result in some gastric distension by exhaled gas. The capnogram shows low initial carbon dioxide concentrations compared with normal recordings, the carbon dioxide disappearing after a few ventilations [62]. Although a virtually normal carbon dioxide waveform after oesophageal intubation in a 10-yr-old boy has been reported, the concentration reduced rapidly after three breaths [101]. Following five ventilatory cycles, oesophageal misplacement should be evident, even when there has been considerable gastric filling with expired air [44]. It should also be remembered that elimination of carbon dioxide depends on cardiac output and pulmonary circulation [23]. Capnography allows very much earlier detection of oesophageal intubation than oximetry, the difference being most marked following preoxygenation [44]. Obviously, oximetry does not identify oesophageal placement of the tube as the cause of desaturation. Continuous display of the capnograph waveform is essential for rapid diagnosis. A device with a chemical indicator for detecting carbon dioxide has been described recently which can be attached between the tracheal tube and the anaesthetic breathing system to confirm correct placement of a tracheal tube [83].

Tactile tests to confirm laryngeal placement of tracheal tubes based on identifying the interarytenoid groove have been described. These have the advantage of not being reliant upon specialized equipment, but the authors stress that familiarity with the techniques is required [28, 29, 51]. An oesophageal detector device has been described which relies upon the relative rigidity of the tracheal wall compared with that of the oesophagus: the oesophagus will collapse over the end of a rigid tube if negative pressure is applied to it, whereas the more rigid trachea will allow free aspiration of air. Reports suggest that this may be a valuable aid to confirmation of correct placement of the tube [76, 82, 115, 118]. However, a false positive result has been reported, with the device suggesting oesophageal placement although the tracheal tube was correctly placed in the trachea; this was caused by the bevel of the tube abutting the posterior tracheal wall [24].

The message concerning possible oesophageal intubation is clear. Clinical signs in determining tracheal tube placement are fallible, the only sure sign being visualization of the arytenoid cartilages posterior to the tube. Preoxygenation may mask the signs of oesophageal intubation by delaying the onset of cyanosis and cardiovascular changes. Considerable suspicion is always required. Removal of the tube and ventilating the lungs using a facemask, or disconnecting the catheter mount and ventilating the lungs using a facemask placed over the open tube and mouth, may be life saving [37, 43, 52, 110].

Aspiration of gastric contents

There is a high mortality with failed or delayed intubation in patients with a full stomach [8]. This is borne out in the *Confidential Enquiries into Maternal Deaths in England and Wales 1973–1984* in which, of the 41 reported deaths associated with difficult tracheal intubation, 37% were caused by inhalation of stomach contents. A characteristic feature is pulmonary aspiration occurring during multiple or prolonged attempts at intubation. In some of these patients, aspiration occurred during maintenance of anaesthesia using an i.v. barbiturate and suxamethonium technique whilst awaiting the arrival of a second anaesthetist. There was failure to appreciate that tracheal intubation and use of neuromuscular blocking agents are not absolute requirements for Caesarean section. All that is required under these circumstances is light general anaesthesia (Guedel Stage 3, Plane 1) with a volatile agent administered by facemask and oropharyngeal airway, where laryngeal reflexes are maintained and passive regurgitation from the stomach is unlikely.

In other cases, failure of cricoid pressure has been implicated when released intermittently to administer oxygen between attempts at intubation, or when incorrectly applied cricoid pressure made intubation difficult. Cricoid pressure is a manoeuvre which requires the patient's head to be held in extension while at the same time one hand of the assistant applies pressure to the cricoid cartilage and his other hand is placed behind the neck to provide counter pressure. If pressure is applied only at the cricoid, the head flexes at the atlanto–occipital joint, making intubation difficult. Trained assistance is required to perform this manoeuvre correctly [35–38]. Should massive regurgitation occur, adoption of the head-down, left lateral position and suction is required. Ventilation with oxygen while maintaining cricoid pressure is not usually a problem, but if it is necessary to release cricoid pressure, this should be done with the patient in the lateral head-down position [32].

Failed intubation drill

Tunstall's failed intubation drill has an established and vital place in obstetric anaesthesia, and should be followed when a decision has been made to abandon attempts at intubation [105, 106, 109]. Mortality is clearly associated with failure to institute such a drill at an appropriate stage [35–38]. Lyons reported a safe outcome for mother and baby in nine patients in whom a failed intubation drill was followed [66]. Cormack and Lehane advocate drills to deal with difficult intubation, failed intubation and the correct use of cricoid pressure, and that training in these techniques should be as thorough as that for managing cardiac arrest [32]. To these may be added a drill to deal with vomiting or regurgitation at the time of induction. Everyone working in the operating theatre, including anaesthetic assistants, surgeons and nursing staff, should be familiar with these drills.

Dark skinned patients

Cyanosis is difficult to detect in dark skinned patients. In one medico–legal audit of mortality and serious morbidity following delayed recognition of oesophageal intubation, five of 12 patients involved were dark skinned [43]. These patients are especially at risk in the event of failed or prolonged attempts at intubation, because severe hypoxia may not be recognized until it is too late. Pulse oximeters are unaffected by skin pigmentation and are of great value in these patients [103]. Pulse oximetry is mandatory in all patients from the commencement of induction of anaesthesia when preoccupation with intubation may detract from monitoring vital signs.

Inappropriate anaesthetic technique

Errors of anaesthetic technique may result in serious complications at intubation, for example, use of an i.v. induction agent and neuromuscular blocking drug in a patient with upper airway obstruction [110].

Tracheotomy and cricothyrotomy

In the 1982–1984 *Confidential Enquiry into Maternal Deaths*, three of the 10 patients reported to have died as a result of difficult tracheal intubation had tracheotomy or an attempt at tracheotomy performed in an effort to provide oxygenation in the extreme circumstances. One patient in whom the tracheotomy failed had an abnormally small larynx and trachea demonstrated at autopsy. The other two patients had short, thick necks and in one the attempted tracheotomy caused haemorrhage into the trachea and lungs [38]. Although an attempt to perform tracheotomy under these circumstances may appear to be reasonable, it is questionable if this is the best choice: the surgeon or anaesthetist may be unfamiliar with the operation; the anatomy may not be straightforward; a lateral position of the patient complicates identification of the landmarks still further; all the correct instruments for performing a tracheotomy may not immediately be available. Furthermore, when the patient is already hypoxic a tracheotomy may take too long to perform. The alternative is transtracheal ventilation of the lungs using a suitably sized needle inserted through the cricothyroid membrane. This is a rapid and relatively atraumatic temporary means of administering oxygen [4].

Spoerel, Narayanan and Singh performed transtracheal ventilation in patients undergoing routine operations, using a 16-gauge needle inserted into the trachea with an intermittent flow of oxygen from a source at 276 kPa [99]. Blood-gas analysis confirmed adequate pulmonary ventilation during periods of 40–75 min. Using a model, they demonstrated also that flows of 400–500 ml s^{-1} could be obtained through a 16-gauge needle by pressurized gas at 276–345 kPa [99]. Different techniques of transtracheal ventilation have been described, and a simple pre-assembled system should be available on every anaesthetic machine to deal with the extreme circumstances which may follow a failed intubation [5, 42, 46, 63, 86, 92, 98, 100].

A simple method (fig. 1) is to use the emergency oxygen flush button as a source of pressurized oxygen. This is delivered from the common gas outlet of the anaesthetic machine via a length of tubing with a Luer–Lok connector for attachment to the needle for tracheal puncture [63, 98]. Although a modified bronchoscope injector system is a suitable alternative source of intermittent pressurized oxygen [60], it may be less universally available. A 12–14-gauge needle (i.d. 2.0–1.5 mm) is the most suitable [5, 42, 46, 63, 86, 98, 100]. A plastic i.v. cannula is unsuitable because it is liable to kink during use. It has been suggested that flows adequate for initial life support can be achieved if a 12-gauge 2.5-cm long cannula is connected to a standard resuscitation bag [100]. As may be expected, the flow of oxygen obtained with this system is considerably less than when oxygen is used at pipeline pressure.

Needle puncture for transtracheal ventilation is performed through the cricothyroid membrane in the midline and the correct position verified by aspiration of air with a syringe (fig. 1) [55]. An artery forceps is clipped onto the needle where it penetrates the skin, to help maintain the correct depth of insertion. Exhalation occurs passively through the upper airway during the intervals between inflations. This is possible because obstruction in the upper airway is usually inspiratory [55]. The operators must ensure that each inflation of the lungs is followed by a deflation. Neff, Pfister and Van Sonnenberg have drawn attention to the complications which may arise as a result of transtracheal ventilation in the event of complete airway obstruction [80]. A sudden increase in tracheal airway pressure occurs as soon as total lung capacity is exceeded, with a concomitant reduction in systolic arterial pressure; severe barotrauma follows. Under these circumstances, apart from an emergency tracheotomy, they suggest ventilation with oxygen using an Ambu bag through a 2.5-mm i.d. transtracheal airway, or spontaneous ventilation through a 3-mm i.d. transtracheal airway, these larger cannulae being required to provide adequate flows [80]. Boulton has suggested a second cannula in

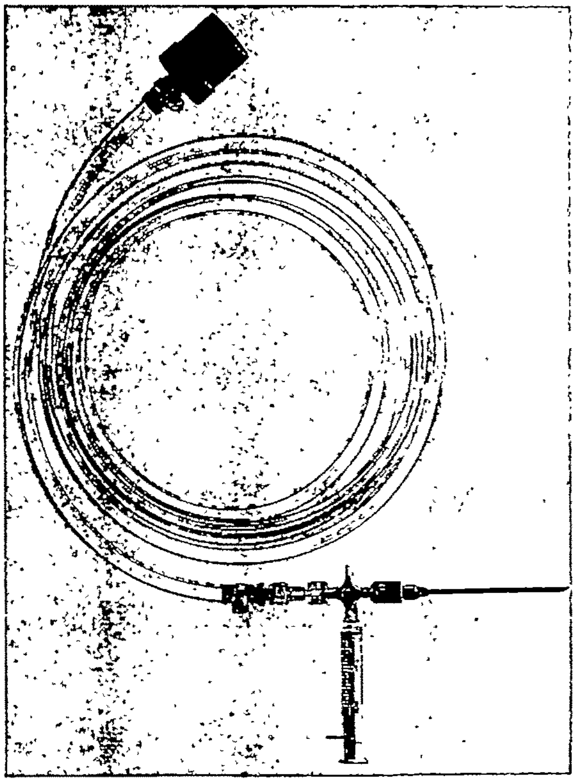

FIG. 1. A simple emergency system for transtracheal ventilation through the cricothyroid membrane. The 12–14-gauge (2–1.5 mm i.d.) needle with the bevel pointing caudally is held in position by attaching an artery forceps where it pierces the skin, after correct placement in the airway is confirmed by aspirating air with the syringe. Ventilation is achieved by intermittently operating the emergency flush oxygen control on the anaesthetic machine. It is vital to check that each inflation of the lungs is followed by a deflation as oxygen escapes through the glottis (see text).

the cricothyroid membrane to act as a safety valve to prevent barotrauma [15]. Transtracheal ventilation with oxygen is a useful temporary measure while emergency tracheotomy is being performed [63]. The simple emergency system described (fig. 1) is inexpensive and easy to apply very quickly. Some commercial emergency cricothyrotomy systems have the advantage that larger diameter cannulae (up to about 7 mm i.d. in adults) can be inserted, thus allowing both inspiration and expiration with spontaneous or assisted ventilation. These include: the Nu-Trake and Pedia-Trake systems (International Medical Devices, Inc., P.O. Box 408, Canoga Park, California 91305, U.S.A.) which comprise a seeking split needle, obturator and tracheal tube airway (adult range: 4.5 mm, 6.0 mm and 7.2 mm i.d.); the Melker system (Cook Critical Care, P.O. Box 489, Bloomington, Indiana 47402, U.S.A.) which comprises a Seldinger technique by which a needle track is dilated to permit the insertion of a 6-mm i.d. tracheal tube; and the Portex Mini-Trach II (Portex Ltd, Hythe, Kent, U.K.) which introduces a standard size 4.0-mm i.d. cannula over an introducing stylet. Another system is the "Quicktrach" emergency cricothyrotomy device (VBM Medizintechnik GmbH, Duiker Ltd, 17 Booth Rise, Northampton, U.K.), which comprises a 4-mm i.d. cannula for adults and a 2-mm i.d. cannula for children. The needle tip is conical and no prior scalpel incision is necessary; an insertion gauge helps locate the optimal depth and hence avoids damage to the oesophagus. The same company produces the Ravussin transtracheal catheter, which comprises a needle and trocar (again without the need for prior incision), over which is a 13-gauge angled Teflon cannula for use in adults (14-gauge for children and 18-gauge for babies); the device has a Luer-Lock connection for attachment to a jet ventilating system in addition to a 15-mm connection for attachment to standard resuscitation bags or breathing systems.

MANAGEMENT OF FAILED INTUBATION

Consider the point at which tracheal intubation has failed, using the standard techniques available in most anaesthetic or operating rooms. Priorities of subsequent management must include maintaining oxygenation and preventing aspiration of gastric contents, bearing in mind those points discussed above which are associated with adverse outcome. Patients may be classified broadly into two groups, depending on the risk of vomiting or regurgitation.

Patients with a risk of vomiting or regurgitation

This group of patients is typified by the obstetric patient in whom both aspiration and hypoxia are likely complications of failed intubation. Tunstall has established the place of a failed intubation drill in obstetric anaesthesia [105, 106, 109]. This entails the following: early implementation of the drill before complications arise; call for senior help; maintaining cricoid pressure, placing the patient in the left lateral position with head-down tilt, and suctioning the pharynx as necessary. Adoption of the left lateral position is important because, should aspiration occur at this stage, only one lung is likely to be affected. Correct insertion of the laryngoscope blade is easy in the left lateral position because the tongue lies inferiorly and does not obstruct the view. Furthermore, compression of the inferior vena cava can be avoided. If adoption of this position is not possible, insert an "Esophageal Gastric Tube Airway" (EGTA); ventilate the lungs with 100% oxygen using a bag and facemask.

Methods to improve the patient's airway include: a combined manoeuvre of extending the head on the neck, opening the mouth and pushing the mandible forward (this may require assistance with bag squeezing); insertion of an oropharyngeal airway; releasing cricoid pressure (only if in lateral head-down position); use of the EGTA device.

If partial airway obstruction is present but sufficient oxygenation is taking place with some return of spontaneous ventilation, persist with IPPV until the patient recovers and then consider an alternative technique (see below).

If the patient has a clear airway there is an option at this stage to establish spontaneous inhalation anaesthesia (Guedel stage 3, Plane 1–2). If necessary, a wide-bore stomach tube (10 mm diameter) may be passed via the mouth with the patient still in the left lateral head-down position, the stomach emptied and antacid instilled (20 ml of sodium citrate 0.3 mol $litre^{-1}$), after which the tube is withdrawn and the pharynx cleared. When spontaneous ventilation has resumed, the patient may be repositioned supine with a left lateral wedge inserted to minimize caval compression. If oxygenation is impossible, perform transtracheal ventilation using cricothyroid puncture. The alternative anaesthetic techniques to be followed if the patient is allowed to recover from the initial induction include: general anaesthesia (inhalation induction) with facemask and spontaneous ventilation; awake intubation and subsequent general anaesthesia; regional anaesthesia; local infiltration; transtracheal ventilation (100% oxygen) with i.v. anaesthesia (etomidate is suggested, with the addition of opioid analgesia after delivery) [105, 106, 109].

In both of Tunstall's original descriptions of the failed intubation drill, he specified the use of oxygen, nitrous oxide and either diethyl ether or methoxyflurane when establishing a spontaneous inhalation technique [105, 106]. In his subsequent description, the agents were unspecified [109]. Rosen described a plan for failed intubation in obstetric anaesthesia which differs from Tunstall's original description in some respects: the patient is not initially turned into the lateral position as this is often impractical and it may be difficult to ventilate the patient's lungs in this position; cricoid pressure is continued at least while the lungs are ventilated; a gastric tube is not passed if it is likely to stimulate vomiting from active reflexes; halothane, enflurane or isoflurane are advocated in preference to ether or methoxyflurane, to establish a technique of spontaneous inhalation anaesthesia [96].

In a case report of failed tracheal intubation in obstetric anaesthesia, Boys described the use of deliberate oesophageal intubation with a cuffed tube [17]. When the cricoid pressure was released, gastric contents were ejected through the tube. Anaesthesia was continued with the oesophageal tube protruding past the side of a face mask. Spontaneous ventilation was used with cyclopropane in oxygen. Remaining gastric contents were aspirated with a suction catheter passed through the tube. Tunstall and Geddes used an EGTA device in an obstetric patient in whom intubation had failed. The patient was obese with the abdomen already open, which precluded turning her into the full lateral position. The EGTA was placed to prevent regurgitation of gastric contents, but the additional benefit of an improved airway was noted [107]. The oesophageal tube displaces the tongue, epiglottis and larynx away from the posterior pharyngeal wall and also creates an adjacent track for the respired gases which results in an improved airway [107, 108]. Corke and Jackson identified a potential hazard with the EGTA caused by the one-way valve within the lumen of the tube at the upper end, which prevents passage of gastric contents out of the tube. This valve may prevent spontaneous decompression of gastric pressure, which would predispose to regurgitation around the cuff. Furthermore, should this tube be passed inadvertently into the trachea and the problem not recognized, the valve would prevent its use for ventilation [31]. Tunstall has modified the EGTA to overcome this problem: the original oesophageal tube is replaced with a Mallinckrodt tracheal tube with a soft cuff allowing its use for ventilation should the trachea be entered accidentally [109].

The Brain laryngeal mask airway [18] has been used successfully after failed intubation at Caesarean section; it is inserted after spontaneous ventilation has resumed. The authors comment that the rules of failed intubation should still apply [27]. Although use of the Brain laryngeal mask has been suggested in obstetric anaesthesia where tracheal intubation is not possible [93], and despite a report of its successful use in a patient with large bowel obstruction and a potentially full stomach in whom tracheal intubation had failed [19], considerable caution is required because the laryngeal mask does not protect against aspiration of gastric contents [20, 25, 33, 34]. Payne studied 50 patients by passing a fibreoptic laryngoscope through the laryngeal mask after insertion and cuff inflation. The oesophagus was visible clearly in three of these patients and this finding has obvious implications for patients at risk of regurgitation and those in whom positive pressure ventilation is required [88]. Brain has suggested the passage of a tracheal tube into the upper oesophagus to allow gastric drainage. The tube should be inserted behind the partly deflated cuff of the laryngeal mask. An alternative option is to attempt intubation of the trachea blindly through the laryngeal mask using an uncut 6-mm cuffed tracheal tube for laryngeal mask sizes 3 and 4 [20]. If the laryngeal mask is used alone, silent regurgitation may be channelled direct from the oesophagus into the trachea without being apparent to the anaesthetist. Certainly, intermittent positive pressure ventilation of the lungs should be avoided if the laryngeal mask has to be used in a patient with a partially obstructed airway and who is at risk from vomiting or regurgitation, because gastric distension may occur and so precipitate regurgitation.

Should tracheal intubation under general anaesthesia fail in a patient at risk from vomiting or regurgitation, subsequent awake intubation followed by general anaesthesia is an alternative option if tracheal intubation must be achieved. This has been an area of controversy because it can be argued that insensitivity of the larynx caused by topical anaesthesia may permit inhalation of gastric contents [112, 95]. Others, however, comment that a fully awake patient with only topical anaesthesia can still protect his airway from aspiration [58]. Ovassapian and colleagues performed oral and nasal fibreoptic intubations in 123 conscious patients considered at high risk from aspiration of gastric contents [84]. Twenty-five of these patients were thought to present difficulty in intubation. Topical anaesthesia was applied to the mouth and pharynx or nasal mucosa as appropriate. For passage of the fibrescope and tube into the larynx, 85 patients had topical anaesthesia applied through the endoscope, 29 had it applied via a cricothyroid puncture, and the remaining patients had no topical anaesthesia. Rigid laryngoscopy was necessary after fibreoptic laryngoscopy failed in one patient suffering haematemesis from peptic ulceration; there were no other cases of regurgitation and no patient had evidence of aspiration. The authors commented that the technique is safest if there is minimal or no sedation, if local anaesthesia is applied through the fibrescope, and if oxygen is administered using a nasal cannula if indicated [84].

An awake fibreoptic intubation in a patient at risk from vomiting or regurgitation with a difficult airway—as indicated by a previous failed intubation—has some advantages: spontaneous ventilation and pharyngeal muscle tone are preserved; the co-operation of the patient is maintained; the situation is now somewhat less urgent for the anaesthetist, although intubation should be completed as soon as possible after topical application of local anaesthesia in order to reduce the risk of aspiration; lower oesophageal sphincter tone is maintained if no sedation is given, with less likelihood of passive regurgitation occurring; patients may be aware of impending vomiting and can assist in turning themselves to the lateral position. Some simple precautions can be taken to minimize the risks of pulmonary aspiration: use topical anaesthesia only, avoiding cricothyroid puncture (no topical anaesthesia should be administered below the vocal cords until the tube is due to be passed, so at least this part of the cough reflex is maintained); no sedation (bear in mind that if intubation under general anaesthesia has just failed, patients may still be drowsy); cricoid pressure may still be applied in the awake patient if it is acceptable and does not in itself induce vomiting; patients may undergo intubation in the sitting position, making regurgitation less likely (familiarity with this approach is required); a second anaesthetist should be present to watch the patient, allowing the intubating anaesthetist to concentrate on the technique.

Patients who do not present a risk of vomiting

In this group of patients there is more time for careful planning of airway management. Efforts are directed towards maintaining a patent airway using conventional oral or nasopharyngeal airways and facemask. The poorly maintained airway in a patient with impending hypoxia obviously requires a different and urgent approach.

If the airway is maintained easily. The anaesthetist must consider if tracheal intubation is necessary, because mask anaesthesia may be preferable to risking further traumatic attempts at intubation [40].

The Brain laryngeal mask airway has been used in both adults and children in whom intubation has failed and represents an important advance in airway management [9, 19]. Blind nasal intubation may be performed through the laryngeal mask if tracheal intubation is deemed to be essential [19, 20]; the same applies to fibreoptic intubation [Hill HM, Silk JM. *The Brain Laryngeal Mask Airway as an Aid to Oral Fiberoptic Intubation.* London: Second U.K. National Fibreoptic Intubation Symposium, 1989; unpublished].

Fibreoptic intubation has been established as a major advance in the management of difficult or failed intubation in the awake patient. If necessary, it may be performed under general anaesthesia with either spontaneous or controlled ventilation [64, 77, 102, 104]. This should also be considered early in the management of failed intubation before multiple attempts with other techniques lead to haemorrhage and oedema in the airway.

Another option is use of the Bullard intubating laryngoscope. This is a rigid fibreoptic system resembling a conventional laryngoscope which comprises a flat curved or duck-billed shaped blade incorporating a fibreoptic light source. It is designed to facilitate rapid visualization of the larynx without requiring alignment of the pharyngeal, laryngeal and oral axes. Tracheal intubation may be accomplished under direct vision; if desired, the integral intubating forceps mechanism advances the tip of the tracheal tube through the glottis by grasping the Murphy "eye". As with all such apparatus, some previous experience is necessary.

Guided blind tracheal intubation (passage of a guide cannula or wire through the cricothyroid membrane, between the vocal cords and out through the nose or mouth) is an alternative technique where intubation has failed. This may also be performed under general anaesthesia if necessary [2, 16, 69, 94, 114], and has been used successfully in a child [13]. Although this technique requires no specialized equipment, it has been superseded largely by fibreoptic methods in developed countries. However, it is still of value when blood in the oropharynx obscures the view.

Two techniques using the rigid bronchoscope have been described. In the first, the bronchoscope is inserted into the trachea, followed by an introducing stylet. The bronchoscope is then removed, leaving in place the stylet, over which a tracheal tube is passed blindly into the trachea [3]. In an alternative technique, the tracheal tube is threaded over a smaller bronchoscope before insertion into the trachea, after which the bronchoscope is removed, leaving the tracheal tube in position [74]. These techniques also have been superseded largely by fibreoptic methods.

Transtracheal ventilation has been used as a routine method of ventilating the lungs of patients with gross pathology such as cancrum oris requiring surgery in the mouth where intubation is likely to be extremely difficult or impossible [59, 61].

Tracheotomy under general anaesthesia is a final option. The indications are governed by the individual patient and the other options available.

If the airway is difficult to maintain. There is always a danger of progressive hypoxia developing when the airway is difficult to maintain following a failed intubation despite the use of oral, nasal or laryngeal mask airways and the priority must be to return the patient to full consciousness. Transtracheal ventilation may be necessary when complete inspiratory airway obstruction exists, until the effects of the neuromuscular blocker and induction agent have worn off. Air issuing through the vocal cords during this procedure may assist in the placement of a tracheal tube [55]. In the majority of patients anaesthesia can be aborted successfully with the use of conventional techniques of oxygenation, after which a technique of elective awake intubation can be planned.

Fibreoptic [30, 73, 91, 104], retrograde guided [1, 39, 45], and rigid bronchoscopic techniques [3] may be performed under topical analgesia with sedation if required. Fibreoptic intubation is now the technique of choice with a high success rate [85], and with least trauma to the patient. An awake technique permits maintenance of spontaneous ventilation and pharyngeal muscle tone and removes the urgency for completing intubation. Elective transtracheal ventilation [59, 61] or tracheotomy under local anaesthesia may need to be considered, depending on clinical circumstances.

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PUPILLARY EFFECTS OF ALFENTANIL AND MORPHINE

C. D. MILLER, A. J. ASBURY AND J. H. BROWN

SUMMARY

We have measured the onset and extent of the miotic effect of morphine and alfentanil in conscious patients. Forty unpremedicated ASA I and II patients were allocated randomly to four groups to receive either i.v. saline (control group), morphine 0.1 mg kg⁻¹, alfentanil 4.0 μg kg⁻¹ or a combination of these doses, and pupil diameters were measured for the next 30 min. There were no significant differences in the control diameters. In the opioid groups, a significant decrease in diameter (about 1 mm), occurred 4 min after administration of the drug and persisted throughout the study. The opioid groups behaved similarly for 25 min. After 10 min the mean diameter of the alfentanil group began to increase, but this did not reach statistical significance until after 25 min.

KEY WORDS

Analgesics alfentanil, morphine. Eye: pupil.

Miosis, analgesia and respiratory depression are typical mu agonist actions of morphine and alfentanil [1]. Changes in autonomic signs, including pupil size, are often used to assess adequacy of anaesthesia. Knowledge of the pupillary response to opioids in the unanaesthetized patient would help in its interpretation. Furthermore, there may be an interaction in the miotic effects when two mu agonist drugs are given in combination. An inhibitory interaction in analgesic effect has been reported when morphine and alfentanil were given in combination to mice [2], and there may be interactions in other mu effects.

Most studies on the effect of opioids on pupillary size have involved anaesthetized patients. However, it is not clear how anaesthetic drugs have contributed to the observed effects.

The object of this study was to determine the onset and extent of pupil diameter changes with morphine and alfentanil in conscious patients. A secondary object was to assess if additional miotic changes occur as a result of an interaction between alfentanil and morphine.

METHOD AND RESULTS

The study was approved by the local Ethics Committee, and all patients gave written consent. We studied 40 unpremedicated inpatients (ASA I and II) undergoing orthopaedic surgery. Patients suffering from eye diseases or receiving medication acting on the eye or autonomic nervous system were excluded.

In the anaesthetic room a cannula was inserted into a vein and routine monitoring commenced. The left pupil diameter was measured using a calibrated pupillometer (accurate to 0.1 mm) which itself provided standard lighting conditions [3].

Patients were allocated randomly to four groups of 10 patients according to the drug administered. Group S received saline 4 ml i.v., group M received morphine 0.1 mg kg^{-1} i.v., group A received alfentanil 4 μg kg^{-1} i.v. and group AM received morphine 0.1 mg kg^{-1} and alfentanil 4 μg kg^{-1} i.v.

Measurements of pupil diameter were made at 0, 2, 4, 6, 8, 10, 15, 20, 25 and 30 min after the injections which were given at time 0. All measurements were made by one of the authors who was aware of the patient's group allocation.

The pupil diameters were analysed using analysis of variance (ANOVA) and Bonferroni's

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correction applied for multiple comparisons, $P < 0.01$ being considered significant. Other data were analysed using paired t tests, and chi-squared tests as appropriate, and $P < 0.05$ was considered significant.

The pooled data mean age was 31.8 yr and pooled mean weight 69.7 kg. The intergroup values for age, weight and frequency of brown eyes were not statistically different. The sex ratios of the groups were different ($P < 0.05$); there was an absence and excess of females, in groups A and AM, respectively.

The pooled monitoring data on all patients during the study showed heart rates of 64–78 beat min^{-1}, systolic arterial pressure of 126–111 mm Hg and ventilatory frequencies of 10.8–15.7 b.p.m.

There were no significant differences between the control pupil diameters in the four groups at time 0 (fig. 1). The main changes in pupil diameter occurred within 4 min of injection in the opioid groups, with minimal change in the saline group. After 4 min the pupil diameter curves in the opioid groups clustered between 2.8 and 3.2 mm. The curve for the saline group exhibited a downward trend, starting above 3.9 mm and decreasing to 3.7 mm over the last 26 min. In addition, after 10 min, the alfentanil group pupil diameter curve began to separate from the other opioid group curves, but this did not achieve statistical significance.

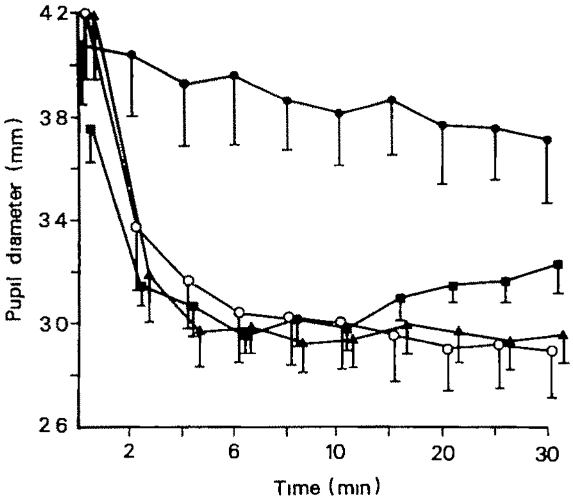

FIG. 1. Mean pupil diameters for each group. The error bars indicate SEM. ● = Saline group; ○ = morphine group; ■ = alfentanil group; ▲ = morphine and alfentanil group.

Analysis (ANOVA) of the pupil diameters in the groups at each time interval after 4 min showed that the three groups receiving opioids formed a population which was statistically distinguishable from any other combination of three groups. In addition, the analysis showed that the groups receiving opioids (A, M, AM) behaved as one homogeneous population for 25 min, which was significantly different from the control group (S) (fig. 1).

COMMENT

The decrease in pupil diameter, about 1 mm, in the opioid groups was almost complete by 4 min. This is interesting, in view of the relatively long onset time of the analgesic action of morphine. This may suggest that miotic effects occur at a lower brain concentration than analgesic actions.

There are few data on the duration of the miotic effect of morphine or alfentanil [4, 5]. Although the effect of alfentanil started to decrease after 10 min, it was still significant at 30 min. As the alpha half-life of alfentanil is about 3 min [6], these results suggest that the miotic effect of alfentanil is not related directly to its plasma concentration. These observations could be explained also by: action of metabolites, specific receptor effects and the polar nature of morphine, which delays its return from the CNS to the plasma.

Continuous measurement of pupil diameter with the pupillometer is unacceptable to patients, because of eye discomfort, but a 2-min measurement interval was acceptable to our patients. Taking this into account, the onset of miotic effect of morphine was similar to that of alfentanil. Unfortunately, the duration of the experimental period precluded estimation of the duration of miotic effects.

Our results do not support the generalization of the hypothesis that there is significant antagonism between morphine and alfentanil [2], at least as far as pupil diameter is concerned. This lack of antagonism could result from interspecies differences in pharmacokinetics and pharmacodynamics, or differences in pain and pupillary control mechanisms. Furthermore, as none of the patients developed pin-point pupils, it is unlikely that the ceiling of opioid miotic effects was reached; therefore, had an important interaction occurred, it would have been observable.

Changes in pupillary accommodation in conscious subjects could increase the variability of pupil diameter measurements; accommodation presumably does not occur during anaesthesia. The pupil diameters in the saline group decreased throughout our study. A similar but less pronounced effect was seen in Asbury's study [3] in anaesthetized patients. We see no obvious explanation for this effect.

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SERUM ACUTE PHASE PROTEINS AFTER ORTHOTOPIC LIVER TRANSPLANTATION

A. M. BURNS, M. P. SHELLY, S. WALKER AND G. R. PARK

SUMMARY

Acute phase proteins were measured in six patients before liver transplantation and for 72 h after orthotopic liver transplantation. The ability of the donor liver to mount an acute phase response was demonstrated, although the response was less than that seen in other groups of patients in whom this has been studied. Because of the reduced response to stress, the value of these measurements as indicators of liver function in this group of patients is limited.

KEY WORDS

Liver: transplantation. Liver function acute phase protein synthesis

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Surgical trauma induces an acute phase reaction in which the liver is stimulated to switch from synthesis of albumin to production of a series of acute phase proteins [1]. These changes include normally a rapid increase in the synthesis of C-reactive protein and α_1-antichymotrypsin, with a consequent increase in serum concentrations. Synthesis of α_1-acid glycoprotein (AAG) is increased also, but to a smaller extent. Serum concentrations of pre-albumin decrease during an acute phase reaction more rapidly than those of albumin, and it may be regarded therefore as a "negative" acute phase reactant.

Immediately after orthotopic liver transplantation, the function of the donor liver is impaired because of the stress of two surgical procedures (donor and recipient) in addition to the cold and warm ischaemic damage sustained during the period between these operations. This study has investigated the ability of the recently transplanted donor liver to mount a stress response and synthesize acute phase proteins, and to assess their value as indicators of liver function immediately after liver transplantation.

METHODS AND RESULTS

The study was approved by the District Ethics Committee and informed consent was obtained before operation from seven consecutive patients. Patients received routine postoperative care in the intensive care unit and had an uncomplicated postoperative course, except for one patient who bled excessively and was excluded from further study.

Serum samples were collected immediately before orthotopic liver transplantation and after operation on arrival in the intensive care unit, then at 4-h intervals over a period of 24 h. Two further samples were collected at 48 h and 72 h. Subsequent analysis for C-reactive protein, α_1-antichymotrypsin, AAG and pre-albumin was performed using specific immunoassay methods [2–5].

Changes in serum concentrations of the acute phase proteins in the 72 h after liver transplantation are shown in figure 1. There was a marked and sustained increase in serum concentrations of C-reactive protein and α_1-antichymotrypsin after surgery. The increase in AAG concentration was not as rapid, with the maximal mean values being just above the upper limit of the normal range. Although serum concentrations of pre-albumin increased after operation, they remained well below the lower limit of the normal reference range.

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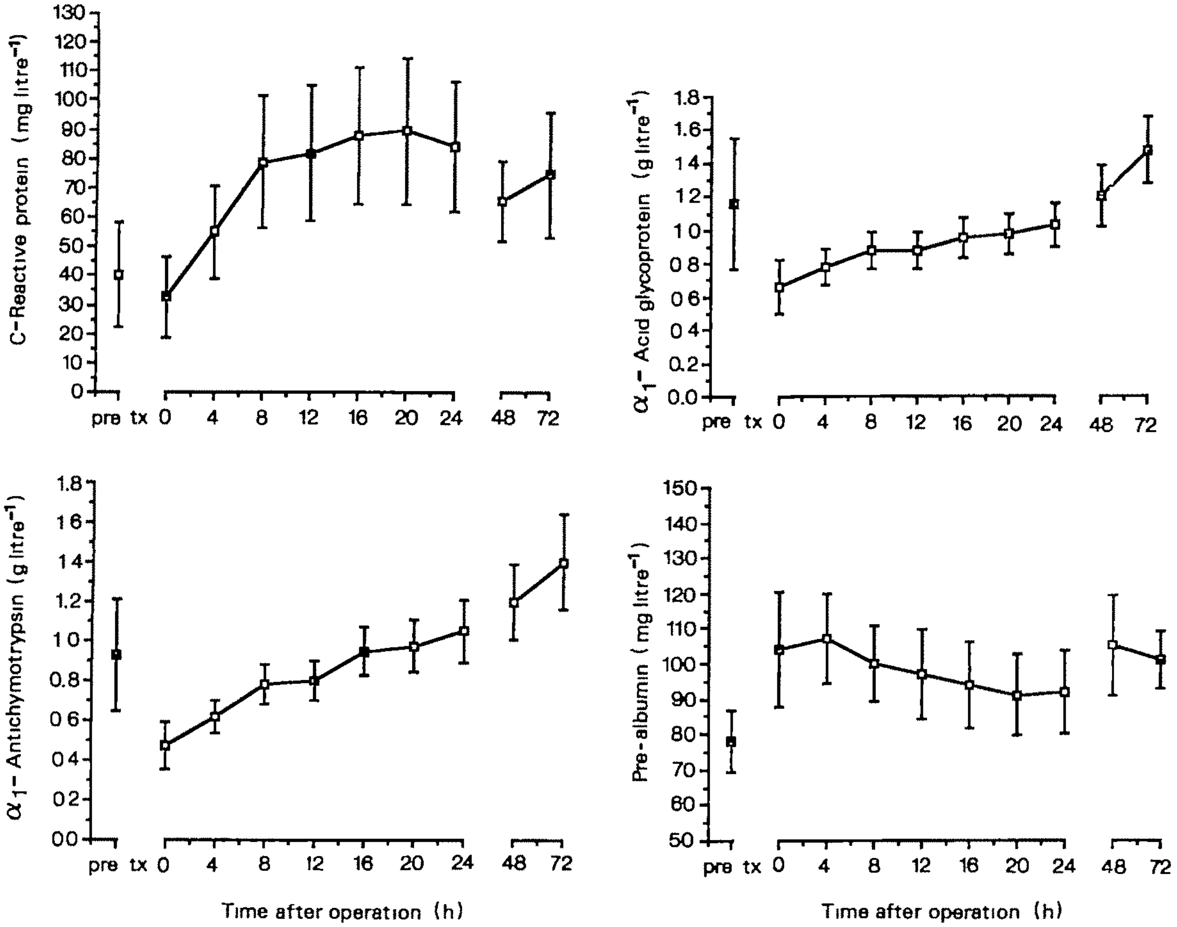

FIG. 1. Mean (SEM) concentrations of the acute phase proteins C-reactive protein (CRP), α_1-antichymotrypsin (ACT), α_1-acid glycoprotein (AAG) and pre-albumin (PA) before surgery (pre) and in the first 72 h after orthotopic liver transplantation (tx) in six patients. Normal ranges: CRP < 10 mg litre^{-1}; ACT 0.35–0.63 g litre^{-1}; AAG 0.5–1.0 g litre^{-1}; PA 150–355 mg litre^{-1}.

COMMENT

Monitoring of liver function after operation is important to detect adverse trends. This is particularly important after liver transplantation in patients who, in addition to the usual problems faced by the critically ill, may have episodes of rejection, infarction or infection. Conventional liver function tests are measured routinely, but alterations in enzyme and bilirubin concentrations may be relatively non-specific, and their interpretation following liver transplantation may be complicated by several factors [6].

Stress is a complex series of metabolic, endocrine and physiological processes. The acute phase response includes the *de novo* synthesis and secretion of proteins by the liver; the rate of production might be used to assess liver function. The stimuli for the hepatocyte to synthesize these proteins, and the underlying cellular mechanisms, are not understood fully and the role of the stress response, particularly its prognostic significance, remains unclear. However, the stress response may reduce tissue injury and promote healing in association with enhanced host resistance [1].

In the immediate period after liver transplantation, when the stress response is still present, serum concentrations of acute phase proteins might be expected to provide an indicator of the synthetic function of the liver, improving liver function being associated with increased serum concentrations of proteins and deterioration with decreased serum concentrations. This study demonstrated that the donor liver appears to be able to synthesize acute phase proteins, despite the ischaemic damage sustained before transplantation. However, the response was less than that reported previously in association with major tissue injury or bacterial infection. The moderate increases in acute phase proteins in our patients may reflect both dilution of the acute phase proteins by transfused blood and ischaemic damage to the donor liver resulting in a less than maximal response. Alterations in liver function may be associated with only minimal changes in protein concentrations and therefore their prognostic value as indicators of liver function is limited. Acute phase proteins may be used to complement conventional liver function tests as a guide to the function of the donor liver. However, further studies are necessary to define their exact role.

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MUSCLE RELAXATION RATES IN INDIVIDUALS SUSCEPTIBLE TO MALIGNANT HYPERTHERMIA

A. URWYLER, F. R. ELLIS, P. J. HALSALL AND P. M. HOPKINS

SUMMARY

Muscle relaxation rate following a tetanic stimulus of adductor pollicis muscle was measured prospectively in 26 patients potentially susceptible to malignant hyperthermia (MH) the day before a muscle biopsy was obtained for MH in vitro *screening. Eleven subjects were found to be MH susceptible (MHS) and 15 subjects MH-negative (MHN). In all patients, relaxation rate was recorded at three different temperatures of the skin overlying adductor pollicis (30, 34 and 38 °C) achieved by a small surface heating unit placed over the thenar eminence. The MHS group exhibited slightly higher relaxation rate at 34 and 38 °C compared with the MHN group and this difference was accentuated with increasing temperature, but was not statistically different. The results of the present study suggest that relaxation rates are normal in MHS individuals under physiological conditions and cannot be used diagnostically for MH screening.*

KEY WORDS

Malignant hyperthermia: muscle relaxation, skin temperature.

Malignant hyperthermia (MH) is an uncommon but serious pharmacogenetic disorder, triggered by volatile anaesthetics and suxamethonium. The only widely accepted diagnostic method for screening MH-susceptible (MHS) individuals at present involves a muscle biopsy followed by both halothane and caffeine *in vitro* contracture tests. This procedure is invasive, time consuming, expensive, and requires special expertise, but none of the alternative diagnostic tests which have been described has been shown to be as reliable [1].

In 1987 Lennmarken, Rutberg and Henriksson reported significantly greater rates of muscle relaxation in MHS subjects compared with controls [2]. Although the population overlap rendered the use of relaxation rate unsuitable as a diagnostic screening test, their findings suggested that MHS subjects differed from MH-negative (MHN) subjects in the way in which they mobilized substrate in the muscle.

Previous work has shown that relaxation rate is both reproducible and independent of sex and age. However, muscle temperature is important, as it correlates linearly with relaxation rate [3]. Fortunately, an acceptable correlation between skin and muscle temperature has been shown which allows for the use of a non-invasive temperature control [4] rather than direct measurement of muscle temperature.

The aim of the present study was to repeat that by Lennmarken and colleagues while attempting to reduce variability by better control of muscle temperature, and to investigate directly the effect of temperature on relaxation rate.

METHODS AND RESULTS

We studied 26 ASA I patients (13 female) aged 20–63 yr. They were admitted for diagnostic muscle biopsy followed by both halothane and caffeine *in vitro* contracture tests. They were either probands or were related to an MHS proband. All patients gave written informed consent to take part in the study, which was approved by the Leeds Eastern Health Authority Ethics Committee. There were 11 patients (six females) in the MHS group and 15 patients (seven females) in the MHN group. Mean ages were 33

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(SD 9) yr and 36 (16) yr, in the MHS and MHN groups, respectively.

Relaxation rate was measured the day before the muscle biopsy on the adductor pollicis muscle of the non-dominant hand after a supramaximal electrical stimulation of the ulnar nerve at the wrist for 1.6 s at 20 Hz, as described previously [4]. The negative electrode was placed distally. Muscle contraction force was recorded using a force transducer (Grass FT 10) connected to a preamplifier (Gould 13-4615-50). Electromyography was recorded using a universal amplifier with an isolated preamplifier (Gould 13-4615-58) to demonstrate supramaximal stimulation. Signals were recorded on a digital storage oscilloscope (Gould 1602) using an automatic trigger, stored in a memory module (Gould 105) and analysed later with a waveform processor (Gould 260).

Skin temperatures over adductor pollicis were measured using an infra-red thermometer (Thermopoint, Agema Sweden). If the initial skin temperature was greater than 30 °C, the lowest temperature at which relaxation rate was measured, the hand was immersed in running cold water for 2–3 min. Warm water which was controlled thermostatically and circulating in a special plastic enclosure, was used to warm the skin overlying adductor pollicis. The time needed to warm up this area from 30 to 34 °C and from 34 to 38 °C was found in preliminary tests to vary between 10 and 20 min. The heating system was removed regularly for measurements of skin temperature and relaxation rate to be made.

Relaxation rate is expressed as % force loss/10 ms calculated from the time to decrease from 90% to 50% of the maximal plateau force (fig. 1). Values increased linearly with increasing skin temperatures (correlation coefficient = 0.999 for both groups). This increase was greater in the MHS than the MHN group, but the difference was not significant (Student's t test). The increase in relaxation rate between 30 and 38 °C (MHS group: $t = 2.698$; MHN group: $t = 2.453$) was significant in both groups ($P < 0.02$), whereas the differences between 30 and 34 °C (MHS group: $t = 1.100$; MHN group: $t = 1.088$) and 34 and 38 °C (MHS group: $t = 1.180$; MHN group: $t = 1.410$) were not (Student's t test, $P > 0.05$).

COMMENT

As we were unable to confirm the previous finding that muscle relaxation rate was abnormally high in MHS individuals [2], this method may not be used as an MH screening test.

Published data of "normal values" for relaxation rate are unreliable, because the technique is not standardized. Different electrical stimulation and recording equipment were used. There was no temperature standardization, and different warming-up techniques were used. In addition, relaxation rate was calculated in a variety of

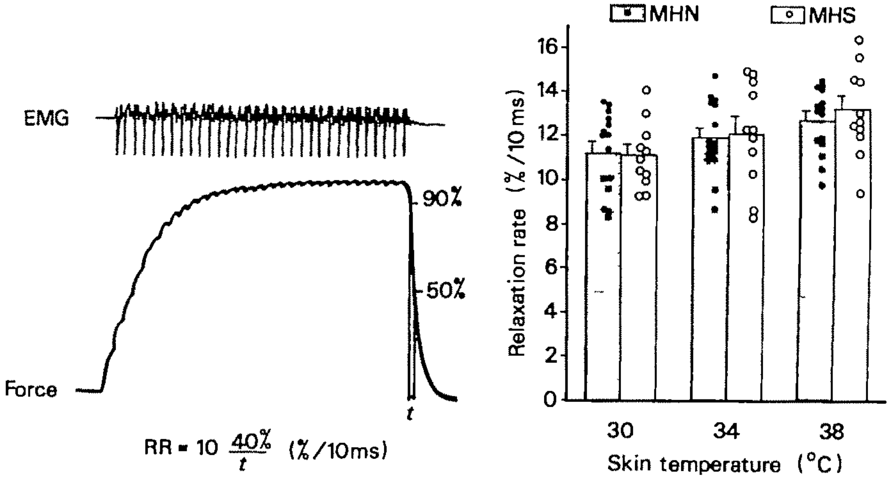

FIG. 1. Electromyography (EMG) and force curve of adductor pollicis muscle developed after supramaximal electrical stimulation for 1.6 s at 20 Hz. Muscle relaxation rate (RR) is calculated from the time to decrease from 90% to 50% of the maximal plateau force. Group means (SEM) and individual results are presented for MHS subjects ($n = 11$) and MHN subjects ($n = 15$) at 30, 34 and 38 °C.

different ways. Although normal values in muscle relaxation rate studies are expected to vary from ours, we cannot explain why Lennmarken's group found differences between MHN and MHS groups, whereas we did not (mean relaxation rate was 12.0% in the MHS group compared with 8.8% in the control group, each expressed as percentage decrease during a 10-ms period [2]).

We have been able to confirm that muscle temperature alters the relaxation rate linearly [3]. In the present study the temperature was controlled rigorously using a surface heating unit over a 10–20 min period, whereas Lennmarken and colleagues used immersion of the hand in warm water at 40 °C for 5 min, followed by an undefined time interval before the investigation of relaxation rate [2]. The temperature of the muscle may not have been at a steady state. However, it seems unlikely that the significantly greater rate of relaxation in MHS individuals in the study by Lennmarken and colleagues was caused by greater muscle temperatures because their mean skin temperatures were 31.1 °C in the MHS and 30.6 °C in the MHN groups, compared with 30, 34 and 38 °C in the present study.

Muscle relaxation is associated with calcium reuptake into the sarcoplasmic reticulum. This process requires ATP, as calcium is pumped actively into sarcoplasmic reticulum. Relaxation rate is related to the rate of energy turnover in the contracting muscle [3]. As increased concentrations of adenylate cyclase were found in MHS subjects, Lennmarken and colleagues speculate that this causes calcium to rebind to sarcoplasmic reticulum faster in MHS muscle, thus increasing the relaxation rate [2]. It could be postulated, however, that in the former retrospective study [2] MHS subjects had been more stressed than the controls and therefore were exhibiting faster substrate cycling and therefore increased relaxation rate. In the present study, however, stress at the moment of the investigation was similar for all patients, as they were all investigated before their MH status was known (all had the muscle relaxation rate investigation on the day before the muscle biopsy). It could be that relaxation rate under physiological conditions should be normal in MHS muscle, because studies using graded physical exercise showed no differences in metabolic muscle response between MHS and MHN individuals [5].

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PIVOTING LARYNX—AN UNUSUAL CLINICAL OBSERVATION AT LARYNGOSCOPY

P. CHARTERS AND A. S. JONES

SUMMARY

Rigid oesophagoscopy was planned in the investigation of a young patient with dysphagia. During laryngoscopy for tracheal intubation an unusual pivoting manoeuvre was required to see the vocal cords. Although the initial diagnostic investigations were unhelpful, follow up directed at explaining the clinical observations led to an eventual diagnosis of anterior tubercles of C6, which explained the observation and accounted for the dysphagia.

KEY WORDS

Anatomy: cervical vertebra, larynx. Complications: difficult laryngoscopy.

CASE REPORT

A 22-yr-old male presented with a 3-month history of a sensation of a "lump around the larynx" and feeling "choked up" in bed at night. He smoked 20 cigarettes a day and also admitted to smoking cannibis habitually. ENT examination was normal, with no neck or laryngeal abnormality. A soft tissue neck x-ray also demonstrated no significant abnormality. The patient was admitted for rigid oesophagoscopy and preoperative assessment revealed slight limitation of extension of the neck and minimal displacement of the larynx from the midline. In addition, a minor degree of hypertelorism was noted. It was thought that laryngoscopy was not likely to be difficult.

Anaesthesia was induced with thiopentone 450 mg i.v. followed by atracurium 35 mg i.v. Although muscle relaxation was considered adequate, only the tip of the epiglottis (i.e. no underlying laryngeal structures) was visible initially at laryngoscopy. Assisted ventilation of the lungs with a face mask was easy. It was possible eventually to see the posterior quarter of the cords, but only after a definitive manoeuvre involving rostral displacement of the larynx followed by firm downwards pressure on its upper margin. Any relaxation of this pressure led to the view being lost immediately. There was a distinct overall impression of the larynx pivoting over a sharp forward protrusion. Tracheal intubation was accomplished and anaesthesia continued uneventfully, but the surgeon had great difficulty with the rigid oesophagoscopy and the procedure was abandoned. A few days later, a flexible oesophagoscopy was performed under local anaesthesia and sedation and was reported as normal.

Because of the pivoting observation, additional x-rays of the neck were performed and reported as "a suggestion of slight subluxation at C5–6 but no other significant abnormality identified on the lateral view". Further assessment by the anaesthetist concerned and comparison with literature search data suggested a diagnosis of anterior tubercles at C6. This was confirmed by computed tomography (CT) scan (figs 1, 2). The slight limitation of neck extension was investigated also, but fusion of the atlas to the occipital bone was not confirmed and the final scan report noted "the odontoid is at the upper limit of normal above McGregor's line [1]".

In view of the patient's continuing symptoms, excision of the tubercles was considered appropriate. At the repeat laryngoscopy for this procedure, not only was the previous need for pivoting observed, but it was also possible to bring the cords into view by movement of the larynx sideways, without rostral displacement. (The scan had suggested this might be possible, as the tubercles lay directly behind the thyroid

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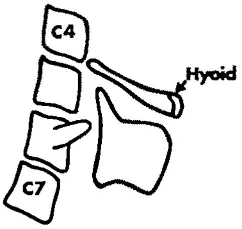

FIG. 1. Line diagram derived from the CT scan and lateral x-rays to show the relationship of the tubercles on C6 to the larynx.

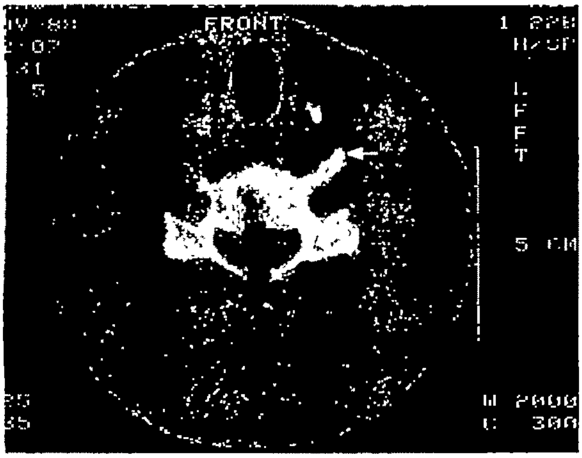

FIG. 2. CT scan at the level of the C6 vertebra in the plane of the axis of the tubercles. In this projection the left appears larger as indicated by the white arrow. The two wings of the thyroid cartilage are directly in front of the tubercles.

cartilage, holding it forward. Moving the larynx sideways did seem to diminish this anterior displacement.)

At operation the tubercles were identified on C6. They arose as narrow protruberances from the lateral border of the vertebral body and projected antero–laterally, and rostrally, toward the rear margins of the thyroid cartilage so as to cause reduction in the normal up and down motion of the larynx. Both tubercles were about 1 cm long by 0.5 cm wide, although on the scan the left had appeared more prominent than the right. (This may have been because of different degrees of anterior angulation.) The abnormal structures were removed without difficulty, using an osteotome. The patient made an uneventful recovery and was discharged on the 6th day after operation. At follow-up 2 months later he was symptom-free.

DISCUSSION

As far as the authors are aware, this observation has not been documented previously. The underlying condition is uncommon and the lateral x-ray signs can be subtle; consequently, as in this case, they may be misinterpreted or overlooked. Lapayowker was responsible for initial radiological characterization of the condition [2], and Applbaum, Gerard and Bryk showed the advantages of CT scan imaging [3] and suggested it is a congenital abnormality analogous to a supernumerary cervical rib. More recently, Nijboer and Penning described tubercles at both C5 and C6 and, from a literature survey, described a pattern of upward development for tubercles on C6 but downward development at C5 [4]. An ipsilateral joint-like articulation has been reported also between the C5 and C6 tubercles.

Many of the patients reported have presented in their early 20s after neck injuries when the findings may have been incidental. Dysphagia, hoarseness and a feeling of a lump in the throat were present in the patient reported by Applbaum. As in our patient, no motility disturbance was evident on barium swallow. In this subject, the preoperative assessment had suggested slight midline displacement of the trachea. A rotation rather than displacement was found on investigation. This occurred because the tubercle on the left protruded more anteriorly than that on the right (fig. 2).

This condition should be differentiated clearly from cervical spondylosis with hypertrophic anterior osteophytes. This is more common, may present with dysphagia [5], and has been reported also as causing difficulty with tracheal intubation because of anterior displacement of the larynx [6]. The pivoting feature would appear to require symmetrical, narrow pointed protrusions just behind the larynx and for this to occur in cervical spondylosis would seem unlikely. Although our patient may be unusual, this report does stress the continuing importance of clinical observations and their appropriate interpretation during anaesthesia.

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EXTRADURAL ABSCESS FOLLOWING LOCAL ANAESTHETIC AND STEROID INJECTION FOR CHRONIC LOW BACK PAIN

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SUMMARY

A case is described of extradural abscess following extradural injection of local anaesthetic and steroid for the management of chronic low back pain. The common signs and symptoms are reviewed, possible causes discussed and the association with diabetes stressed.

KEY WORDS

Anaesthetic techniques. extradural. Complications: extradural abscess.

Extradural abscess is an uncommon illness with an incidence of 0.2–1.2 per 10000 hospital admissions [1]. We report the occurrence of an extradural abscess, following extradural injection with local anaesthetic and steroid. As far as we are aware, there has been only one similar previous case report: in that case an extradural abscess followed a single injection of triamcinolone acetonide into the lumbar extradural space [2].

CASE REPORT

A 65-yr-old woman with non-insulin dependent diabetes presented to the Pain Management Clinic with chronic right sided low back pain. The pain was aggravated by movement and radiated to the right hip and thigh. One month earlier, she had been admitted to another hospital where a surgical cervical sympathectomy had been performed for causalgia of the right arm. This was complicated by right phrenic nerve palsy, a staphylococcus (*S. aureus*) septicaemia and wound abscess.

Examination revealed an obese lady with signs of a peripheral sensory neuropathy affecting both lower limbs. There was tenderness over the lumbar facet joints bilaterally, although facetal compression (lateral flexion and extension) caused no increase in the pain. Straight leg raising was 70° on the left and 60° on the right.

A clinical diagnosis of mechanical low back pain was made, and the patient was prescribed diclofenac 50 mg three times a day, doxepin 10 mg at night and a course of three lumbar extradural injections of local anaesthetic and steroid was arranged to be carried out at 1-week intervals.

Two weeks later, the patient attended for her first lumbar extradural injection, which was performed at the L4–5 interspace with the patient in the sitting position. Using an aseptic technique, the extradural space was identified with loss of resistance to normal saline and 0.25% plain bupivacaine 6 ml and methylprednisolone 80 mg was injected through an 18-gauge Tuohy needle.

Her pain improved for 2 days, but then recurred. Using a similar technique, a second extradural injection was performed at the L3–4 interspace with 0.25% plain bupivacaine 8 ml and methylprednisolone 80 mg. There was another good early response, but after 4 days the pain recurred, although not to its initial extent. One week later a third extradural injection was performed in the same manner as the second.

Three weeks later the patient presented to another hospital with left hip, thigh and knee pain following a fall 1 week earlier. She was able to walk only with difficulty and was noted to be tender along the lateral aspect of the left hip, thigh and knee. X-rays of the lumbo-sacral spine showed osteoporosis and old degenerative changes. She was treated with rest and paracetamol with codeine phosphate tablets.

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She re-presented the next day with back pain which she claimed had been present for several days. It was sufficiently severe to have required treatment with i.m. pethidine the night before. It did not radiate and there was no associated paresthesiae. On examination, she was afebrile. There was tenderness to palpation over the L2–5 spinous processes. Straight leg raising was 20° on the right and 30° on the left. Knee reflexes were absent, the ankle reflexes normal and the plantar reflexes demonstrated flexion. The bladder was palpable. Lumbar spine x-rays demonstrated no new changes; haematological investigation revealed a haemoglobin concentration of 9.1 g dl^{-1}, white cell count of 15×10^9 $litre^{-1}$, with 76% neutrophils, and an erythrocyte sedimentation rate (ESR) of 95 mm h^{-1}. Serum creatinine concentration was 249 μmol $litre^{-1}$ and blood sugar 9.6 mmol $litre^{-1}$. The patient was observed for 24 h then discharged.

The patient presented again the next day and was admitted with increasing pain in her back, radiating down the left hip and thigh. She was not distressed while lying quietly in bed, but any attempt to examine her caused severe back pain. Her back was tender from L2 to L4, straight leg raising was equal on the left and right, at 45°. Power, sensation and reflexes in the lower limbs were recorded as normal. Her temperature was 38.2 °C.

Investigations now revealed haemoglobin concentration 7.8 g dl^{-1}, white cell count 19 $\times 10^9$ $litre^{-1}$, with 93% neutrophils, and toxic granulation with left shift on the blood film. Serum concentration of sodium was 128 mmol $litre^{-1}$, chloride 84 mmol $litre^{-1}$, urea 42.8 mmol $litre^{-1}$, creatinine 286 μmol $litre^{-1}$ and blood sugar 13.4 mmol $litre^{-1}$. Liver function tests were marginally abnormal. Urine microscopy revealed a large number of white cells and culture resulted in a growth of *Proteus mirabilis* of more than 10^5 bacteria per high power field. Blood cultures grew *S. aureus*. A bone scan was normal.

Treatment was commenced with i.v. cephotaxime and flucloxacillin and two units of blood were transfused. By the following day she had developed a tender distended bladder, was unable to void urine and the bladder was catheterized. There was little change in her general condition over the next 3–4 days.

Six days after admission a myelogram was performed through an L3–4 dural puncture which yielded purulent cerebrospinal fluid (CSF) with a white cell count of 0.9×10^9 $litre^{-1}$ and a red cell count of 0.0016×10^{12} $litre^{-1}$. *S. aureus* was cultured from the CSF. The myelogram demonstrated an oedematous cauda equina and decreased CSF space. Post-myelogram computed tomography identified an extradural abscess compressing the spinal cord and occupying most of the spinal canal from L1 to L5.

The patient was transferred to this hospital and underwent urgent decompressive laminectomy. At operation there was an extensive extradural abscess from T12 to L5. The paravertebral muscles from L1 to L5 were inflamed and there was free pus in the interspinous space at L3–4. Laminectomy was performed from T12 to L5, and the pus and extradural fat removed.

The postoperative period was complicated by ventilatory failure requiring prolonged ventilatory support. In the 7th week after operation, the patient was discharged from the intensive care unit. She still had bladder dysfunction requiring continued catheterization and was unable to walk because of marked weakness of both lower limbs. She died 2 weeks later, after deterioration in renal function. Postmortem examination was not performed.

DISCUSSION

Extradural abscess is a rare but recognized complication of extradural anaesthesia. Some cases described earlier occurred following continuous caudal anaesthesia, at a time before emphasis on sterile techniques [3, 4]. More recently, extradural abscess has followed extradural catheter insertion [5–8], spinal anaesthesia [9, 10] and infiltration of local anaesthetic into the sacro-coccygeal area [11].

Symptoms from extradural abscess are often subtle [12], with both presentation [13] and diagnosis delayed, sometimes until irreversible neurological signs are present. Important diagnostic features include fever, severe back pain, localized spinal and paraspinal tenderness and leucocytosis. Late signs include nerve root weakness and paraparesis [1, 12]. Myelography and post-myelography computed tomography or magnetic resonance imaging confirm the diagnosis. Treatment involves antibiotics and urgent decompressive laminectomy.

Small haematomata may develop following needle or catheter insertion into the extradural space and this may act as a site for bacterial growth. Infection may be introduced in several ways. At the time the procedure is performed, if the technique is poor the needle may transport bacteria from the skin to the extradural space. There may be contamination of injected substances, especially if multidose ampoules are used. Spread may occur also from an adjacent locally infected area such as rib, vertebral body or paraspinal muscle. However, the most likely source of infection is haematogenous spread from furunculosis [1]. The commonest organism cultured is *S. aureus*.

In our patient, it is possible that the extradural space was contaminated with *S. aureus* during the septicaemia that followed cervical sympathectomy and that presentation of the abscess was merely delayed. However, the operative appearances of liquid pus and inflammation of the paravertebral muscles and interspinous space suggested an acute rather than a chronic abscess.

The controversy surrounding extradural analgesia in febrile obstetric patients was reviewed by Davies and colleagues in 1988 [14]. Bacteraemia occurs in up to 9.7% of these patients, but the incidence of extradural abscess is extremely small and is not increasing, despite the increased use of extradural analgesia during labour, delivery and the postoperative period. This may be because *S. aureus* is rarely involved; indeed, two recently reported cases of bacterial meningitis in parturients after extradural anaesthesia involved streptococci as causative organism [15].

Diabetes mellitus appears to be a risk factor in development of extradural abscess. In two reviews [1, 12] involving a total 74 cases of extradural abscess, not associated with extradural injections, 14 patients were identified as having diabetes mellitus. In 1989 Chan [2] reported extradural abscess in a diabetic subject following extradural injection of steroid for sciatica. The association between spinal or paraspinal infection and diabetes has been noted previously and a suggestion was made that if an increased ESR were found in a diabetic patient with backache, specific investigation for spinal or paraspinal infection was warranted [16].

It has been shown that extradural steroids can suppress the hypothalamic–pituitary–adrenocortical axis, which may lead to immunosuppression [17] and this may have been an additional factor contributing to abscess formation in our patient.

This case emphasizes the need for particular caution in diabetic patients and for a high index of suspicion of paraspinal infection when back pain and signs of infection co-exist following extradural injection.

Since this case, we have reviewed our management of diabetic patients and now make a careful examination for occult infection, including measurement of ESR, before performing invasive therapeutic procedures.

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PROLONGED PARALYSIS FOLLOWING SUXAMETHONIUM AND THE USE OF NEOSTIGMINE

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SUMMARY

A case of prolonged neuromuscular block following the administration of suxamethonium is reported. Three hours after administration of suxamethonium, a well defined, recovering phase II block was demonstrated with a T4:T1 ratio of 0.25, and neostigmine was administered. Although the T4:T1 ratio was improved to 0.9, T1 remained at 25% of control, and significant paralysis persisted which responded to administration of cholinesterase. It is concluded that neuromuscular monitoring cannot reliably predict reversibility in such cases and that, even after 3 h, antagonism of prolonged suxamethonium block should commence with cholinesterase, followed by neostigmine if necessary.

KEY WORDS

Antagonists, neuromuscular relaxants: cholinesterase, neostigmine. Neuromuscular relaxants. suxamethonium

Prolonged paralysis following the use of moderate doses of suxamethonium may be produced by either a marked reduction in the serum concentration of cholinesterase or abnormal forms of the enzyme. In the latter case, the genetic defect results usually in a greater prolongation of the action of suxamethonium than reduction in plasma concentration of cholinesterase. Where prolonged neuromuscular block occurs, it is accompanied frequently by a change in the character of the block from a depolarizing to a phase II type of block, with some of the characteristics of a non-depolarizing form of paralysis [1]. When this occurs, there is some debate on whether or not the non-depolarizing component of the block should be antagonized with anticholinesterases [1]. We report a patient in whom neuromuscular function was monitored continuously during prolonged paralysis following suxamethonium and in whom neostigmine was used in an attempt to antagonize the block.

CASE REPORT

The patient was a 45-yr-old man weighing 65 kg, undergoing elective partial gastrectomy for persistent duodenal ulceration. Preoperative evaluation revealed no significant abnormalities and the patient gave no history of anaesthesia-related problems. One of us (H.C.H.) had anaesthetized this man on three previous occasions, using spinal anaesthesia, extradural anaesthesia and a general anaesthetic technique using a long-acting neuromuscular blocking drug. No complications were encountered during any of these procedures. The patient was receiving no medications, and was not premedicated.

Following preoxygenation, anaesthesia was induced with thiopentone 425 mg followed by suxamethonium 100 mg and cricoid pressure applied, as there was a risk of partial pyloric obstruction. The trachea was intubated and anaesthesia maintained with 70% nitrous oxide and 1% halothane in oxygen; two bolus doses of alfentanil 2 mg were given incrementally during the procedure. Before induction of anaesthesia, a Datex Relaxograph neurotransmission monitor was applied to the left forearm. This device monitors the evoked EMG in the hand and displays the train-of-four (TOF) ratio on a continuous print-out, T1 as a percentage of the pre-block baseline (established before induction in this case) and the T4:T1 ratio. Non-depolarizing neuromuscular blockers were with-

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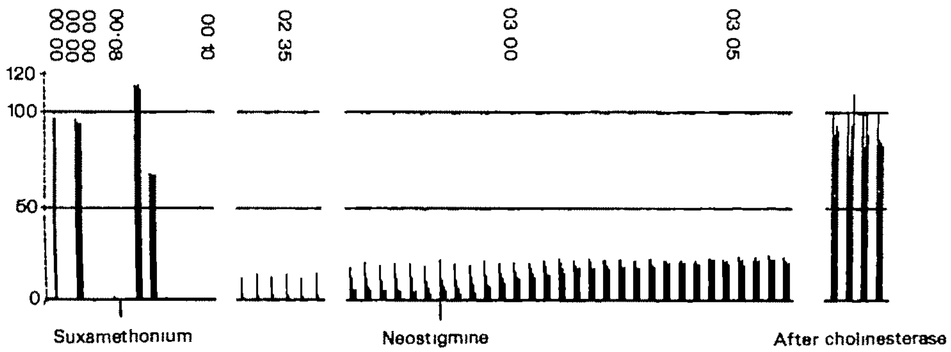

FIG. 1. EMG traces. Neostigmine was administered 2 h 58 min after suxamethonium, and cholinesterase 32 min later. The poor quality of the trace following the administration of cholinesterase was caused by excessive patient movement.

held pending recovery of neuromuscular transmission from the suxamethonium block. There was no recovery from the block for 110 min following administration of the suxamethonium and, thereafter, recovery began to occur very slowly. After a further 60 min, it was apparent that a non-depolarizing type of block was present, with marked TOF fade being seen on the twitch monitor (fig. 1). At this time, T1 was 25 % of the control value and the T4:T1 ratio was 0.25; the operation had almost ended. In view of these findings and the considerable time elapsed since administration of suxamethonium, it was decided to attempt to antagonize the neuromuscular block and therefore neostigmine 2.5 mg was administered, accompanied by atropine 1.2 mg. This resulted in complete antagonism of the TOF fade (T4:T1 ratio 0.9), but T1 remained markedly reduced, at 25 % of control. Thirty minutes later purified cholinesterase 45 mg was given as it was thought that the plasma concentration of neostigmine would be sufficiently low at this time not to interfere significantly with the action of the administered cholinesterase. Within a few minutes, T1 had increased to 75 % of control and the patient was able to sustain good ventilatory function without assistance. The tracheal tube was removed and the patient made an uneventful recovery, progressing rapidly to T1 100 % of control. Subsequent investigation showed the patient to have no detectable cholinesterase activity, a serum concentration of cholinesterase 295 u litre^{-1} (normal range 3500–8500 u litre^{-1}), and to be genotypically homozygous for the silent gene.

DISCUSSION

The management of prolonged paralysis following suxamethonium is much debated. In 1956, Brennan [2] described the dual action of suxamethonium and concluded that neostigmine had a definite place in the treatment of prolonged apnoea following suxamethonium. The use of neostigmine was questioned subsequently by Vickers [3], who suggested that neostigmine should be withheld until there was clear evidence of development of fade, and that anticholinesterases should not be administered earlier than 90 min after administration of suxamethonium. There has been much subsequent discussion of the topic, and Baraka [4] concluded that there must be a broad spectrum where both depolarizing and desensitization block coexist to differing degrees, and that in this phase, neostigmine enhances the block; when desensitization is fully established, neostigmine may be used to antagonize the block. The degree of antagonism was claimed to be proportional to the degree of desensitization. In an extensive review, Lee and Katz [5] stated that an established phase II block could be diagnosed by the presence of a TOF ratio of less than 0.4, and suggested that antagonism with an anticholinesterase could be attempted if the TOF ratio was less than 0.4 and that recovery had been observed for 20–30 min.

The decision to use neostigmine in the present patient was based on the well established phase II block that had developed, and the fact that 3 h had elapsed since administration of suxamethonium. The administration of neostigmine antagonized completely the TOF fade, but made no difference to the T1 value, and did not improve neuromuscular transmission. From our survey of the literature, the use of neostigmine so long after the administration of suxamethonium has not been reported previously. Most reports suggest that neostigmine should be usable after an interval in excess of 90 min, provided that significant TOF fade is established. This report shows conclusively that this is not the case. It is concluded, therefore, that even after as long as 3 h after administration of suxamethonium, sufficient suxamethonium (or possibly the monocholine derivative) may persist to maintain a block unresponsive to neostigmine. The prompt recovery of neuromuscular transmission in this patient following the administration of cholinesterase strongly supports the recommendation of Viby-Mogensen [6] that this should always be the first line of therapy, but with the rider that no time considerations should apply. When the cholinesterase has been given, this may be followed by neostigmine if necessary to antagonize any residual phase II component not antagonized by the cholinesterase, as this may otherwise persist for 30 min or more [6].

ACKNOWLEDGEMENTS

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FOAM CUFFED TRACHEAL TUBES: CLINICAL AND LABORATORY ASSESSMENT

K. J. POWER

SUMMARY

The efficiency of a foam cuffed tracheal tube has been studied in protecting the pulmonary tree from aspiration of oropharyngeal and gastric contents. Following instillation of methylene blue dye above the cuff, subsequent fibreoptic bronchoscopy revealed no instance of dye staining of the tracheal mucosa. A "bench" study was undertaken subsequently to estimate the likely pressure that the cuff would exert on the tracheal mucosa as a result of elastic recoil properties of the foam. The results suggested that, under normal clinical conditions, the pressure is not likely to exceed a value at which impairment of the mucosal blood supply would occur.

KEY WORDS

Equipment: cuffs, tracheal tubes. Complications: aspiration.

The inflatable cuff of a tracheal tube serves two functions: it should seal the airway to prevent aspiration of pharyngeal contents and permit leak-free positive pressure ventilation. Excessive inflation of cuffs is a well known cause of morbidity because of impairment of the blood supply to the tracheal mucosa [1]. Despite this, measurement of intracuff pressure is not commonly practised during routine anaesthesia. A postal questionnaire to members of The Intensive Care Society of The United Kingdom [2] revealed that cuff pressures were measured in only 17% of units.

Attempts to solve this problem have been directed to the use of low-pressure, high-volume cuffs. However, these large volume cuffs inevitably develop folds when placed in the trachea, and Seegobin and Van-Hasselt have demonstrated 100% incidence of dye aspiration past the cuffs of three different tubes of this type [3]. Whilst evidence of dye aspiration should not be equated with clinically significant pulmonary aspiration [4], the results indicate that these cuffs are not sealing the trachea.

The concept of foam cuffed tracheal tubes is not new [5], but they did not enter widespread clinical use. However, they are now marketed widely as the Bivona "Fome-Cuff" tracheal tube (fig. 1). The foam-filled cuff is evacuated for passage into the trachea. When correctly placed, the cuff is connected to the breathing circuit by means of a pilot tube and the foam cuff expands to seal the airway. The danger of excessive pressure damage to the tracheal mucosa should be minimized as the cuff is not inflated by the operator and any increase in intracuff pressure caused by diffusion of nitrous oxide is equilibrated with the airway via the pilot tube.

The aim of this study was to evaluate the performance of this tube in protecting against aspiration of pharyngeal contents and to obtain an estimate of the pressure that the cuff might exert on tracheal mucosa.

PATIENTS AND METHODS

An open study was performed in 20 patients (nine male) undergoing orthopaedic procedures and requiring tracheal intubation. All patients gave informed consent to the study, which had been approved by the local Ethics Committee. Following induction of anaesthesia and muscle relaxation, an evacuated and lubricated foam cuffed tracheal tube was inserted (size 8.0 mm i.d. for women and size 9.0 mm i.d. for men). Following insertion, the pilot tube of the cuff was connected to the airway by means of a T-piece attached to the proximal end of the tube (fig. 1), to equilibrate

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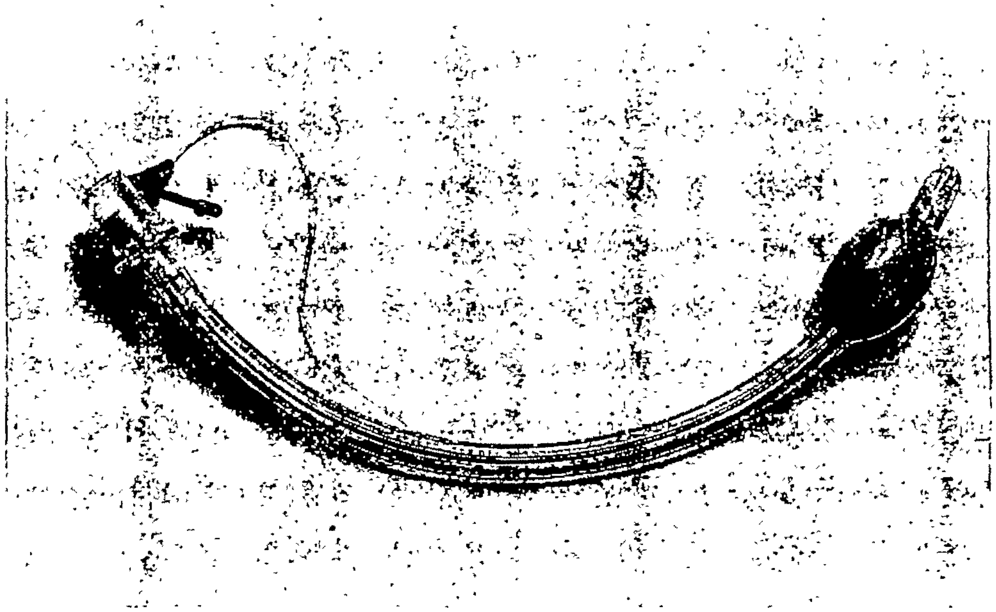

FIG. 1. Foam cuffed tracheal tube with cuff expanded and pilot tube attached to T-piece connector.

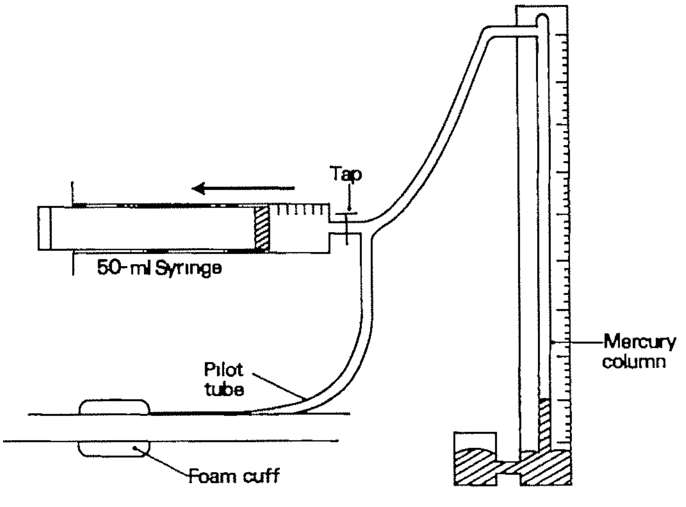

FIG. 2. Apparatus to determine the recoil pressure of the foam cuff at different volumes of air evacuated.

intracuff pressure with the airway pressure throughout the ventilatory cycle. After the pilot tube is connected to the airway, the foam cuff expands almost instantaneously.

When the patient's lungs had been inflated manually to ensure that there was no apparent leak, methylene blue dye 1.5 ml was placed above the cuff of the tracheal tube using a plastic quill. The patient underwent either mechanical ventilation ($n = 15$) by means of a Manley ventilator or was allowed to breathe spontaneously ($n = 5$).

Towards the end of the procedure, whilst the tube was still *in situ*, the tracheal mucosa was inspected via a flexible fibreoptic bronchoscope for evidence of dye aspiration past the cuff of the tube.

Before extubation the air was evacuated from the foam before withdrawing the tube. This

TABLE I. *Bronchoscopy results following instillation of methylene blue*

No.	Mean age (yr)	Duration of intubation (min)	Dye seen at bronchoscopy: Totally clear	Minimal on tube	Mucosal staining
Mechanical ventilation					
6M	45	137	4	2	0
9F	63	106	7	2	0
Spontaneous ventilation					
3M	34	65	2	1	0
2F	52	45	1	1	0

TABLE II. *Pressure differences across cuff wall (from outside to inside) for a range of volumes of air within the cuff (mean (SD) of 10 tubes of each size)*

	Volume of air (ml)	Pressure diff. (mm Hg)
Size 8.0 mm i.d.		
(Mean volume of air required to effect seal = 5.5 ml)	1	35.1 (2.66)
	3	30.9 (2.12)
	5	27.0 (1.84)
	7	24.4 (1.69)
	9	21.7 (1.42)
	11	20.3 (1.59)
	13	18.9 (1.37)
	15	18.1 (1.43)
	17	16.9 (1.36)
	19	15.6 (1.01)
	21	13.3 (1.10)
	23	8.2 (0.72)
	25	0
Size 9.0 mm i.d.		
(Mean volume of air required to effect seal = 8.0 ml)	1	37.9 (2.59)
	3	32.5 (2.16)
	5	28.2 (1.83)
	7	23.8 (1.47)
	9	20.6 (0.93)
	11	18.0 (0.89)
	13	13.9 (0.70)
	15	0

volume of air was noted and a mean value obtained for the volume of air drawn into each size of cuff to effect a seal.

The pressure that the cuff exerts on the tracheal mucosa bears a relationship to the elastic recoil of the foam and this is an inverse function of the volume of air drawn into the cuff to effect a seal (see Appendix). Therefore a "bench" experiment was conducted using a Poddy mercury manometer. Air was aspirated from the cuff in increments of 2 ml and the resulting recoil pressure noted (fig. 2). From this, it was possible to produce a table relating the volume of air aspirated from the cuff and the subsequent recoil pressure of the foam.

RESULTS

Passage of the tube was satisfactory in all subjects and there were no episodes of air leak or cuff rupture during the trial.

Fifteen patients underwent bronchoscopy after mechanical ventilation and five after spontaneous ventilation. There was no evidence of dye staining the tracheal mucosa below the tube. In six patients a feint blue discolouration was observed below the level of the cuff on the tube, but it was not possible to differentiate this from light reflected from above. If it did represent leakage, it was insufficient in amount to stain the tracheal mucosa itself. There was no difference in the performance of the 8.0-mm and the 9.0-mm tubes (table I).

Table II shows the results of the experiment with the Poddy mercury manometer. The recoil pressure was maximal when the cuff was deflated fully and was related inversely to the volume of air drawn in to effect a seal.

DISCUSSION

The results of this study suggest that the use of a foam cuffed tracheal tube may offer protection against aspiration. The technique of placing the dye directly above the cuff is similar to that described by Seegobin and Van-Hasselt [3] and Petring and colleagues [6] and affords a more severe test of the integrity of the seal compared with other studies in which the dye has been placed in the oropharynx [7, 8] or on the back of the tongue [9].

There is a considerable literature on the incidence of silent regurgitation and aspiration [3, 6, 9–11]. Red rubber tubes with low volume cuffs inflated to effect a seal appear to offer protection [3, 7], but at the expense of high intracuff pressures which would result in cuff to tracheal wall pressures (c–t pressures) greatly in excess of the capillary perfusion pressure of the tracheal mucosa (20–30 mm Hg [1, 12, 13]). The usual response to this problem is to use tubes with low-pressure, high-volume cuffs in circumstances where prolonged intubation is required. However, a recent study [3] demonstrated a 100 % incidence of dye positive aspiration using three different tubes of this type.

It is not established to what extent minor degrees of aspiration contribute to the morbidity of postoperative and intensive care patients. Dye aspiration does not signify evidence of clinically significant aspiration [4], but it has been suggested that up to 20% of postoperative pulmonary complications may be caused by silent aspiration [14]. It has also been suggested that tracheal colonization is the result of aspiration in 30% of patients in the ITU [15].

Long term ventilation with overinflated air-filled cuffs may cause occlusion of the blood supply to the tracheal mucosa which may subsequently result in tracheal stenosis. For high-volume, low-pressure cuffs, it has been shown that the pressure exerted by the cuff on the tracheal wall approximates to the intracuff pressure [16]. However, even these cuffs may be overinflated and are still subject to pressure increases caused by diffusion of nitrous oxide through the cuff wall [17]. The pilot tube principle of the foam cuff tube permits the intracuff pressure to be equilibrated with the airway pressure throughout the ventilatory cycle whilst maintaining an adequate seal [18]. Use of this tube should obviate the need for measurement of cuff pressures or the use of pressure regulating devices such as the Cardiff Cuff Controller [19].

When a foam cuff is used, the *average* c–t pressure is a function of the elastic recoil of the foam [20] and of mean airway pressure. As an example in this study, consider the 8.0-mm cuff with a maximum capacity of 25 ml. To evacuate 14 ml of air such that 11 ml remains within the cuff requires a negative pressure of 20.3 mm Hg; thus if a fully evacuated cuff is allowed to expand with 11 ml of air to effect a seal, there is a positive recoil pressure of 20.3 mm Hg which is exerted as a mean pressure on the tracheal mucosa.

This does not imply, of course, that the pressure over the entire tracheal mucosa in contact with the cuff at all points is always 20.3 mm Hg. The less compliant anterior trachea is subject to greater pressure than the more compliant posterior wall and pressures may increase during coughing. Furthermore, folds and wrinkles in the cuff material may result in areas of localized high pressure, but this should occur only if too large a tube is used, thereby permitting only minimal expansion of the foam. However, as shown previously [3], it is the folds in the cuff material which permit dye positive aspiration in low-pressure, high-volume cuffs. As there were no episodes of aspiration in this study, it is reasonable to assume that localized pressure problems caused by folds in the cuff material should be minimized.

A reduced incidence of tracheal dilatation has been reported in dogs subjected to ventilation for prolonged periods via a foam cuffed tube [20]. This has been explained on the basis of the increase in calibre of the trachea with positive pressure ventilation leading to expansion of the foam cuff, but a reduction in mean recoil pressure exerted.

Several studies [5, 13, 21] have attempted to measure c–t pressures exerted by foam cuffed tubes, but all have failed to state the degree of expansion of the foam when the measurements were taken. Furthermore, the measurements are dependent on the model and method used; none is entirely satisfactory [22]. However, as observed in this and another study [21], considerable pressure may be required to evacuate the foam fully and it is important to select a tube of appropriate size, to ensure a reasonable degree of foam expansion. The advantage of the foam cuff is that it may permit measurement of the volume of air expanding the foam and relate this (from table II) to a recoil pressure which reflects the mean c–t pressure.

In summary, it would appear that the foam cuffed tracheal tube may offer protection against aspiration, whilst exerting a pressure on the tracheal mucosa that is acceptable and predictable. The chief indication for a tube of this type would be for patients who require or are likely to require long term tracheal intubation and ventilation.

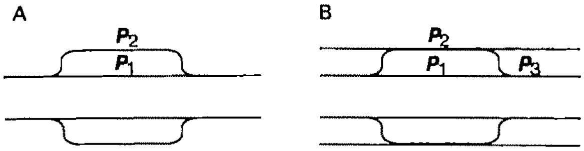

FIG. 3. Pressures inside and outside the foam cuff. A: In the laboratory experiment. B: In use.

APPENDIX

The volume of gas in the cuff is a function of the pressure difference across the cuff wall (table II). In the bench experiments, the pressure outside the cuff (P_2) was atmospheric; the pressure inside (P_1) was negative (fig. 3A). In clinical use, the pressure inside (at end-expiration and in the absence of PEEP) is approximately atmospheric. At the ends of the cuff, a small area is exposed to a pressure, P_3, which is also approximately atmospheric. Therefore, any longitudinal recoil pressure from the foam is taken up by distension of the ends of the cuff. However, most of the wall of the cuff is in contact with the tracheal mucosa. Therefore, assuming negligible distension of that part of the wall, the pressure applied to most of the outside of the cuff is that exerted by the tracheal wall on the cuff (and hence by the recoil pressure of the foam on the tracheal wall) (P_2) (fig. 3B).

Therefore, for any given cuff volume, the pressure difference ($P_2 - P_1$) during use (fig. 3B) is similar to that during the bench experiment, and the pressure on the tracheal mucosa approximates to the sum of that pressure difference and the airway pressure—subject to the caveats in the main text about the effects of the trachea not being a uniform cylindrical tube.

W. W. Mapleson

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CORRESPONDENCE

AXILLARY BRACHIAL PLEXUS BLOCK: CHOICE OF TECHNIQUE?

Sir,—I would like to add to the discussion of the excellent review by Brockway and Wildsmith concerning the factors which influence axillary brachial plexus block [1]. I use and teach the Winnie perivascular technique [2], advancing the tip of a short-bevelled needle as far centrally as possible, maintaining digital pressure over the axillary artery distal to the injection site, and returning the arm to the patient's side following needle withdrawal so that the head of the humerus does not impede the upward flow of local anaesthetic [3].

Whilst working in the U.S.A., I was taught that palpation of a "hot-dog" in the axilla following injection of local anaesthetic implied successful injection into the brachial plexus sheath, whereas a "hamburger" indicated a subcutaneous injection and probable failed block. My own, seemingly natural, addition to the Winnie technique has been to maintain digital pressure over the artery after the arm has been returned to the side, and with the fingers of the opposite hand massage the "hot-dog" towards the axilla until it is no longer palpable. The pressure of these fingers is continued for 5–10 min.

For the past 4 years I have taught this technique to visiting anaesthetists attending the annual Bristol Regional Anaesthesia Techniques course. I use a volume of 40 ml and, until the second advent of prilocaine, I used 1.25% lignocaine with 1:200000 adrenaline. I felt that this was the maximum concentration of lignocaine that should be used when teaching trainees who are about to attend examinations, in order to keep within a safety margin of 7 mg kg^{-1} for an adult. Each arm was tested for completeness of sensory block below the elbow and supplementation used where necessary. Each year I performed one of the blocks, but otherwise blocks were undertaken by the course participants. Over the 4-yr period, there were 20 (69%) completely successful blocks, of which eight were for surgery in the radial nerve territory. In three patients whose block was supplemented by light general anaesthesia, two blocks were for carpal tunnel release in patients with rheumatoid arthritis who had previous operations which were undertaken under general anaesthesia (table I).

The results of this short series are not outstanding, but the technique is sufficiently reliable in inexperienced hands that it continues to be taught as the method of choice.

L. E. Shutt
Bristol

TABLE I. *Success of axillary brachial plexus block amongst Bristol Regional Anaesthesia Techniques course participants 1986–89. LCNF = lateral cutaneous nerve of forearm; MCNF = medial cutaneous nerve of forearm*

Sensory block below elbow	Nerve territory of surgery					
	LCNF	MCNF	Radial	Median	Ulnar	Total (%)
Complete		3	8	8	1	20 (69)
Incomplete + wound supplement	1			2		3
Incomplete + nerve block at elbow	2			1		3
Incomplete + GA				3		3
Total	3	3	8	14	1	29

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BODY TEMPERATURE AND ANAESTHESIA

Sir,—"Body Temperature and Anaesthesia" [1] reviews conventional opinion on the cause and prevention of surgical hypothermia. However, recent work on environmental heat exchange [2] suggests that the authors' recommendations for preventing hypothermia are insufficient.

Body temperature decreases when heat loss exceeds heat production which, under general anaesthesia, is about 40 W m^{-2} (1 W = 3.6 kJ h^{-1}). The authors have calculated heat loss as the change in body heat content of a two-compartment model [3]. However, this model has never been validated in surgical patients, especially those in whom a major body cavity is exposed to the environment [4]. In our experience, based on the direct measurement of heat loss, the model fails to estimate heat loss accurately in surgical patients. Nevertheless, the model contains an important clinical concept: that body heat is distributed unevenly between a "core" and a "shell". This implies that "normothermia", a normal core temperature, does not guarantee a normal body heat content. The "afterdrop" in core temperature that follows cardiopulmonary bypass rewarming is a common example of uneven heat distribution.

We have measured environmental heat exchange directly with Heat Flux Transducers [5] and have confirmed the published values for heat exchange coefficients [2, 6–8]. The combined coefficient for the principal mechanisms of heat loss, radiation and convection, at air velocities $\leqslant 0.2$ m s^{-1}, is 10 W m^{-2}/°C of temperature gradient between the patient, or his coverings, and the environment. Therefore, for a gradient of 10 °C, the heat loss by radiation and convection alone is 100 W m^{-2}. This is much greater than the 10-W m^{-2} heat loss (67 kJ h^{-1}) quoted in this review.

If heat production supplies 40 W m^{-2}, but environmental heat loss is 10 W m^{-2}/°C, it is not surprising that the lower limit of the "thermoneutral" zone is 28 °C [9]. A 4 °C gradient from skin to environment maintains skin temperature in the "thermal comfort" range (32–34 °C) [10] and allows heat loss to balance heat production so that core temperature remains steady. However, this temperature imposes a thermal load that most surgeons do not accept as, while the patient is uninsulated (0.2 clo insulation units), the surgeon is heavily insulated (1.5 clo) and produces more heat.

As a first step, it would be more practical to insulate patients correctly. Surgical coverings reduce heat loss by 10–20%, while formal insulation materials (one layer of "Thinsulate" = 1 clo) can reduce heat loss by 57%. To be completely effective would require insulation of at least 2 clo. Other environmental factors are important: increased air velocity (laminar flow systems) markedly increases convective and evaporative losses, while radiant heat from operating lights decreases radiative losses but increases evaporative losses [11].

Warming and rapidly infusing i.v. fluids prevents their imposing a thermal load, but neither offsets environmental heat loss nor reverses an existing body heat deficit. If anaesthetic gases are 100% humidified at 42 °C, with all the risks this entails, heat is saved by preventing evaporation and gained by condensation. However, for core temperatures from 37 °C to 20 °C, the sum of the heat saved and the heat gained is only 1.3 W m^{-2}/litre of minute ventilation. Compared with the environmental loss, this is insignificant.

The heat supply of a warming mattress is limited by skin conductance, temperature gradient and contact area. One model can supply 41 W m^{-2}/°C [2, 6] and therefore has the potential to double the heat available to a patient. The ability of this to maintain core temperature depends on the magnitude of the environmental heat loss. The potential heat supply of the heating equipment now available, expressed in W m^{-2}/°C, is: warming mattress = 41; radiant heater = 7; hot air mattress at 0.2 m s^{-1} = 4.

The solution to the problem of surgical hypothermia lies in determining the patient's thermal balance by directly measuring heat production and heat loss. This allows the development of both appropriate thermal models for surgical patients and practical and effective methods to prevent surgical hypothermia.

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SIR,—Thank you for the opportunity to reply to the letter from Drs English and Scott.

We agree that the two-compartment model of body heat is a simplification which has its limitations, some of which were discussed in our article, and applaud the efforts of Drs English and Scott to measure cutaneous thermal flux directly using heat flux transducers. However, this methodology has never been applied to surgical patients, and the particular configuration of transducers used by Drs English and Scott has never been validated as giving an accurate measure of total cutaneous heat flux [1].

Drs English and Scott maintain that a patient under general anaesthesia can tolerate only a 4 °C temperature gradient with the environment because of poor insulation and a reduced metabolic rate. Accepting that heat production under anaesthesia is about 40 W m^{-2} (144 kJ m^{-2} h^{-1}, 34.3 Cal m^{-2} h^{-1}) and assuming heat loss by other routes is minimal, thermal stability with a 4 °C temperature gradient would require insulation of approximately 0.65 clo (0.49 °C kJ^{-1} m^{-2} h^{-1}; 0.117 °C Cal^{-1} m^{-2} h^{-1}).

A naked man in still air has a surface insulation of 0.2–0.75 clo depending on the degree of vasoconstriction present [2]. The layer of air around the body supplies another 0.8 clo [2] and surgical drapes might reasonably be expected to provide a further 0.5 clo (the same as a teeshirt and shorts). This total insulation of 1.5 clo would permit thermal stability in the presence of a 9.3 °C temperature gradient, and if the theatre is maintained at 24 °C the skin temperature could be 33 °C, that is in the middle of the thermal comfort zone.

We appreciate that many factors may have an adverse effect on this state of affairs (theatre ventilation systems, open wounds and wet surgical drapes would all reduce the tolerable temperature gradient); however, the above calculations serve to demonstrate that thermal balance may not be upset as badly as suggested. Indeed, the combination of warm i.v. fluids, heated humidified inspired gases and unwarmed towels to increase patient insulation resulted in *increases* in mean skin temperatures, core body temperature and calculated total body heat in patients undergoing intra-abdominal surgery [3, 4]. We would wholeheartedly endorse efforts to increase the thermal insulation of patients undergoing major surgery, especially if the operating theatre temperature is low, but other methods of minimizing heat loss must not be neglected.

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POSTOPERATIVE PATIENT-CONTROLLED ANALGESIA

Sir,—I should like to comment on the Proceedings of the Anaesthetic Research Society in which Thomas, Heath and Rose reported a study of the effects of psychological variables and pain relief system on postoperative experience of pain [1].

I have used Cardiff Palliators for patient-controlled analgesia (PCA) for virtually all my patients having major surgery since 1984 at Lewisham Hospital. I was a participant in the first of the current trials on the use of PCA for postoperative pain relief at Lewisham Hospital.

In common with Thomas, Heath and Rose, my experience has been that, where the PCA machine is offered to a patient after operation, without adequate explanation, adequate pain relief can still be achieved by the patient.

The suggestion in this paper is that psychological testing may permit patients with a high level of anxiety and neuroticism to be provided with postoperative analgesia, when a department is unable to provide each patient with PCA technology, and is of benefit in these circumstances. However, I believe that this should only be a temporary expedient in the development of PCA usage, within an individual department.

My experience has been that the ability to offer PCA to every patient requiring major surgery, and liable to require considerable amounts of analgesics following surgery, carries a major benefit in improvement of coping exhibited by these patients before operation. Most patients comment favourably on the availability of PCA, and those who have had previous surgery with traditional techniques of postoperative analgesia are particularly enthusiastic about the technique.

As PCA allows the patient to choose whatever pattern of postoperative analgesia they require, one can reliably assure the patient of the technique's success.

I believe that every Department of Anaesthesia should have a sufficient number of machines to allow all patients requiring major surgery to have PCA available for their use.

J. M. Cundy
Lewisham

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1. Thomas VJ, Heath ML, Rose FD. Effect of psychological variables and pain relief system on postoperative pain experience. *British Journal of Anaesthesia* 1990; **64**: 388P–389P.

Sir,—Thank you for allowing us the opportunity to comment on Dr Cundy's letter. We would be the first to acclaim his enthusiasm and effectiveness in introducing PCA to Lewisham Hospital, without which our study would not have taken place. We, too, hope that every patient for whom PCA is suitable could be assured the use of a machine. The unpalatable fact is that we have not achieved this, and many hospitals do not have one machine. Lewisham Hospital's original Cardiff Palliators are well over 6 years old; patients in our studies all used modern equipment kindly loaned by the manufacturers, but we are still having difficulty obtaining funds for purchasing new machines.

Our aim was to show who might benefit most when insufficient machines are available—a situation that we believe all hospitals will go through as they build up experience and equipment. A necessary element of the design of these studies was that patients would not receive prior information about the postoperative analgesia regimen. Preliminary analysis of the results yields the interesting incidental finding that patients' pain relief was comparable to that found in other trials in which great stress was laid on the need for prior familiarization with the equipment. Further, no patient in our studies has failed to use the machine, although it has been suggested to us that almost 5% of patients will not "push the button". It seems at least possible that a few patients may be frightened by preoperative information. Our reaction to this has been to devise a patient information sheet designed to be informative and reassuring to patients. Time will show if high acceptability rates can be maintained in this way.

Finally, while we feel proud that anaesthetists have been leaders in this field, there is no reason why the cost of the equipment should compete with anaesthetists' other legitimate needs; the benefits of PCA (after those to the recipient) extend into nursing and the surgical specialties (earlier mobilization and reduced length of stay). The equipment should be treated as general hospital equipment purchased from Unit funds, recognizing its major contribution to overall quality of care.

V. J. Thomas
M. L. Heath
Lewisham

British Journal of Anaesthesia 1990; 65: 441–442

BOOK REVIEWS

Lectures on Anesthetics and on Asphyxia (English translation of 1st Edn). By C. Bernard (translated by B. R. Fink). Published by The Wood Library-Museum, Park Ridge, Illinois, with the concurrence of J. B. Baillière, Paris. Pp. 404; illustrated. Price $35.00.

Leçons sur les Anesthésiques et sur l'Asphyxie was published first in 1875 and is based on a series of lectures given by Claude Bernard whilst Professor of Medicine at the College de France in Paris, during 1869. This work, by the man known as Mr Physiology to his contemporaries, has not received widespread recognition in anaesthetic circles, which tend only to recognize his contributions to research which elucidated the site of action of curare. This regrettable state of affairs has been corrected by the superb translation of Bernard's work by Raymond Fink, and publication by the Wood Library-Museum of Chicago.

There is an introductory translator's preface which reviews Bernard's career and achievements and places the work in the context of European research of that era.

There is an introductory chapter on the blood and the *milieu interieur* which provides the framework of physiology on which the subsequent lectures are supported. His concise explanation of the circulation and respiration are excellent. There follow 10 lectures on anaesthesia, with a chapter dedicated to each. The first gives a historical review of anaesthesia and how the agents are used. It gives detail of variation in effect between species and advocates particular routes of administration. The second chapter expands these ideas on different routes of administration: gastrointestinal, subcutaneous, via serous surfaces and via the lung are all reviewed, and the basic distribution pathway via the blood is explained. The third lecture describes the current theories of the mode of action of anaesthetic drugs, and these are continued in lectures four and five. This last chapter concludes with an explanation of anaesthetic death and methods of reversing the effects of accidents caused by chloroform.

The sixth chapter moves away from inhalation anaesthesia and reviews the effects of opioids in some detail. The seventh describes the use of opium in physiological experimentation on animals. Lecture eight refers to the advantages of opium premedication which is then followed by chloroform maintenance. This is expanded in the ninth chapter, whilst the final lecture on anaesthesia reviews the effects of chloral in anaesthetic practice.

The second part of this book is composed of a further eight lectures on asphyxia. Chapter one defines the various types of asphyxia and shows inter-species variability to lack of oxygen and reviews other historical work on the subject. The second chapter explains absorbtion of coal fumes and discusses effects of carbon monoxide. These are expanded in lectures three, four and five. Lecture six gives greater details of the effects on the blood of inhalation of carbon monoxide, while chapter seven refers to elimination of the gas and the differentiation between the effects of carbon dioxide and those of carbon monoxide. The final chapter in this series of lectures gives greater details on the physiological changes in venous and arterial blood during asphyxia.

There are then a series of four appendixes. The first is on experimental studies of opium and its alkaloids, the second on apomorphine, the third is on chloral hydrate and the fourth reviews the hazards of cast iron stoves and carbon monoxide production. There is, finally, an extract from a series of lectures on the phenomena of life common to animals and plants, which reviews the properties of protoplasm.

The book as a whole is a delight. The chapters on anaesthesia were perhaps more interesting to this reviewer than those on asphyxia. It provides an eminently readable insight into Bernard's understanding of physiology related to anaesthesia and asphyxia. Each lecture is built up through a series of reasoned arguments based on animal experiments, which were performed during the lecture. It provides a wealth of well referenced historical data which will be a must for any anaesthetist with an interest in how their specialty has evolved. I believe that it can be likened to John Snow's scientific approach to anaesthesia which is so often referred to by current historians.

Raymond Fink and the Wood Library-Museum should be congratulated on an excellent addition to current knowledge, not the least of which is the detail that it is best to avoid chloroform when attempting physiological research on the horse as, should the experiment fail and the horse perish, the chloroform absorbed into the tissues will render the animal totally unsaleable for food because of its bitter taste!

D. Wilkinson

Yearbook of Anaesthesia, 1989. Edited by R. D. Miller, R. R. Kirby, G. W. Ostheimer, M. F. Roizin and R. K. Stoelting. Published by Year Book Medical Publishers, Inc., Chicago, London, Boca Raton. Pp. 369; indexed. Price £40.

The *Yearbook of Anaesthesia, 1989* is the most recent in a series which has been published regularly (approximately annually) for several years. It is also part of a large parallel family of yearbooks in other subjects, this book having a total of 35 companion volumes for 1989. The contents follow a format similar to those of previous years: a collection of monographs, each with respect to one published original article and followed by a short commentary from an "expert". The monographs are grouped by subject into chapters and sections and the book is fairly comprehensively indexed.

It is likely that the main aim of this book is to assist the general anaesthetist to keep abreast of current topics without having to attempt to read all of the original literature. The monographs are extracted from a total of 86 publications and it is probably impossible for every anaesthetist who wishes to stay informed to scan all of that literature. Herein, however, also lies one of the principal weaknesses of the book, namely that the reader can only read those articles which have been chosen for him and trust the selectors that those are the most important articles for him to read. This degree of subjectivity is a major drawback, although the editors must realize this, as they do state in their Introduction "We have attempted to select those articles which are especially important..." With the plethora of world literature it is probably impossible to give a fully balanced view.

The expert comments are on the whole helpful, but it might have been better to introduce a little more uniformity to them. They vary from one word (which is not really helpful) to one page.

Overall, this book will be of some use to the practising anaesthetist who does not have time to read the journals and can thus obtain an overview of selected parts of the world literature. It will have only limited use to those more directly involved with research, as they should already be familiar with the literature as it applies to their fields, or be in a position to explore more easily any new fields which they desire.

The book is, unfortunately, marred by a few careless mistakes. In particular, Chapter 14 should presumably read "management of *chronic* pain" and not "management of *cardiac* pain". In addition, the journals *Anaesthesia and Intensive Care* and *Anaesthesia* are spelt incorrectly.

B. J. Pollard

Clinical Anaesthesiology, International Practice & Research, Volume 2, Number 3: Fluid Resuscitation. Edited by W. J. Kox and J. Gamble. Published by Baillière. Pp. 760; indexed; illustrated. Price £18.50.

Clinical Anaesthesiology, International Research & Practice (previously known as *Clinics in Anaesthesiology*) is published three times a year. Each issue is devoted to a topic of contemporary relevance and is intended to keep anaesthetists informed of any recent developments in that subject.

This issue is devoted to the subject of Fluid Resuscitation and is divided into three main sections. The first section considers the applied physiology and pharmacology involved in the management of shock. This includes brief but concise chapters on the microcirculation and Starling force manipulation, cardiovascular responses to tissue injury/haemorrhage, and the effects of fluid loading and vasoactive drugs on circulatory responses. A moderate knowledge of basic science is assumed, but the reader is rewarded with an improved understanding of some difficult concepts such as pressure–volume loops and the relationship between mean systemic pressure, cardiac output and central venous pressure.

Types of fluid replacement therapy are described in the next section, which begins with a balanced and unequivocal exposition of the colloid–crystalloid controversy, emphasizing the importance of haemodynamic and oxygen transport patterns in prediction of outcome. Interesting and competent discussions on the place of artificial oxygen carriers and the use of small volume resuscitation follow, in addition to the perennial subjects of nutrition/metabolism and haemostasis.

The adverse effects of fluid resuscitation provides the theme for the third section. The inevitable yet unresolved arguments for and against the use of microfilters (i.v. fluid filters and blood filters) are given a fair hearing. The administration of plasma substitutes is complicated infrequently by allergic reactions and difficulties with blood typing and cross-matching In addition, their use is thought to have some adverse effects on reticulo-endothelial function. The mechanisms and clinical importance of these problems are described in the next three contributions. The putative mechanisms involved in reperfusion injury, which itself may result in ischaemia and multi-system dysfunction, are described in detail. The last chapter considers the treatment of the overhydrated patient, including the use of combination diuretics, peritoneal dialysis, intermittent isolated ultrafiltration and continuous therapies (SCUF and CAVHD). This represents the most lucid account of the subject that has appeared in the anaesthetic literature.

The number of specialist, postgraduate update publications has increased substantially in the past few years. Some are published as books and others are in the format of the glossy journal. The quality varies considerably and this depends on many factors.

The guest editors and contributors of this issue of *Clinical Anaesthesiology* have succeeded in producing a book that is both readable and stimulating. It contains much important information that the practising anaesthetist will find invaluable. The choice of contributors is inspired and results in a balanced and enlightened handling of a traditionally difficult subject. Highly recommended.

D. A. B. Turner